

*Textbook of
Pharmacology for Dental and
Allied Health Sciences*

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Textbook of Pharmacology for Dental and Allied Health Sciences

SECOND EDITION

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Textbook of Pharmacology for Dental and Allied Health Sciences

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***Dedicated to
My beloved mother
Mrs. Lalitha Narayan***

Foreword

It is a daunting challenge to a studious student of a subject to write a textbook. This is particularly so in case of pharmacology, a subject having tremendous potential for expansion.

Medicine is said to be the most dynamic amongst biological disciplines; pharmacology can be said to be so amongst health science disciplines. It has stupendously grown in its own right and on its own wicket. In addition, it has been quick in responding to advances in other disciplines. Ramification of pharmacology into various other disciplines has resulted in mutual sharing of knowledge and impetuous for further study. This has resulted in the continuing growth of both factual and conceptual knowledge-base, too rapid and huge to comprehend. These facts weigh on the mind of a studious student.

A textbook for undergraduate students has to be clear, lucid, comprehensive and concise. This requires a critical and shrewd sifting and sieving of the vast data, to pick-up those that are necessary and relevant in a given context. Such a job demands grit, knowledge, ability and prudence. Dr (Mrs) Padmaja Udaykumar, a young pharmacologist has gratifyingly demonstrated these in her venture of writing a textbook in pharmacology for students of dental, physiotherapy and allied branches of health sciences.

Most textbooks on this subject contain data and information that suit medical students. But many student-groups of other streams of health sciences require knowledgeability in the subject pharmacology in a way that is meaningful and relevant to their respective field. Indeed pharmacology is one of the core-subjects in these courses. This point in view, the author has made a commendable attempt in this direction.

Need for condensation of the vast data inevitably makes the text and approach more catalogic and less thematic. Yet there is enough factual data as well as sufficient thematic message synchronized, a very important point in a text for undergraduates.

Dr Padmaja Udaykumar has brought out a concise book in pharmacology with clear and comprehensive coverage of the topics in a systematically organized manner and presented in a simple—‘easy to read and grasp’ style. This book though primarily meant for dental, physiotherapy and nursing students, it contains enough material to be useful even for medical students, particularly for quick revision.

Teacher, like parent, gets proud pleasure at the progress and deserving achievements of the next generation. I did derive such pleasure while going through the text of this nice book by Dr Padmaja Udaykumar and say a few words about it.

Prof DR Kulkarni

Head of the Department of Medical Education

BM Patil Medical College, Bijapur

Former Principal, DY Patil Medical College, Kollapur

Former President, Indian Association of Pharmacologists

Preface to the Second Edition

Pharmacology is a subject that has been rapidly growing. To keep pace with it, books in pharmacology need to be updated frequently. The book has been thoroughly revised with appropriate additions, deletions and tailored to the needs of a dental student. In response to the feedback received, wherever applicable, the relevance of the topic to a dentist has been highlighted. More figures, charts and tables have been added and the book is brought out in multiple colours, all of which make it more student-friendly. Many universities have introduced 'Compare and Contrast', between related drugs in the question papers. Therefore a series of 'Compare and Contrast' have been given in all relevant chapters. Keeping in mind the burden on students, efforts have been made to include only the necessary things and prune the unwanted ones. A chapter on **emergencies in dental practice** has been included as required by some universities.

The First edition of the book was titled 'Short Textbook of Pharmacology for Dental and Allied Health Sciences' and has been renamed in the second edition as *Textbook of Pharmacology for Dental and Allied Health Sciences*.

I hope the book makes learning pharmacology a pleasurable experience.

Please send your feedback to raaguday@rediffmail.com.

Padmaja Udaykumar

Preface to the First Edition

Pharmacology is a science that forms the basis for modern medicine. It is a rapidly changing field with new drugs being constantly introduced. The knowledge of pharmacology is important for all those who deal with drugs apart from medical practitioners. But the depth could vary. The need was felt for a short textbook for Dental, Nursing, Physiotherapy and other health science students. Hence this book was brought out, keeping in mind the size of the book and information required.

General pharmacology has been discussed in detail as it forms the basis for understanding pharmacology. Similarly chemotherapy, particularly general chemotherapy, analgesics, anaesthetics and corticosteroids are dealt with in adequate depth. Mechanisms of action have been discussed in brief. In each chapter, the prototype drug has been discussed in detail while the differing features of others are then mentioned. Simple figures have been used wherever necessary. Common drug interactions are given in the Appendices. Accepted abbreviations have been used. References for further reading are mentioned at the end of the text. The chapter on Dental Pharmacology is included. Adequate importance has been given to essential drugs.

I hope this book serves to make pharmacology easy for the students of Health Sciences.

Padmaja Udaykumar

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I wish to express my sincere thanks to Prof. D.R. Kulkarni for writing Foreword to this book and for his valuable guidance.

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I also thank my colleagues Dr. Vijayalakshmi M., Dr. Princy, Dr. Prasannalakshmi, Dr. Manohar Revonkar and Miss Deepa for their support. I am extremely thankful to the management of Fr. Muller Medical College—Director Fr. Baptist Menezes, Administrators Fr. Lawrence C D'Souza, Fr. Dennis D'Sa and Dean Dr. Sanjeev Rai for their encouragement.

I wish to thank Dr. Prasanna Kumar J. Asst. Professor in oral medicine for his help.

I owe a special note of thanks to my husband Prof. Udaykumar K. for his constant encouragement, valuable suggestions and support in this endeavor.

I thank Jaypee Brothers Medical Publishers, New Delhi for bringing out this colourful book.

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Section 1

General Pharmacology

1

Introduction and Sources of Drugs

HISTORICAL ASPECTS

Pharmacology is the science that deals with the study of drugs and their interaction with the living systems.

The useful and toxic effects of many plant and animal products were known to man in ancient times. The earliest writings on drugs are the Egyptian Medical Papyrus (1600 BC). The largest of them, Ebers Papyrus lists some 800 preparations.

In early days there was a close relationship between religion and treatment of diseases. The knowledge of the use of drugs often rested with the priest or holyman. Drugs were thought to be magical in their actions.

Several cultures like the Chinese, Greek, Indian, Roman, Persian, European and many others contributed a great deal to the development of medicine in early times. The drug prescriptions included preparations from herbs, plants, animals and minerals. In the middle ages many herbal gardens were cultivated particularly by monasteries.

Though medicine developed simultaneously in several countries, the spread of knowledge was limited because of poorly developed communication across the world.

India's earliest pharmacological writings are from the 'Vedas'. An ancient Indian physician Charaka and then, Sushruta and Vagbhata, described many herbal preparations included in 'Ayurveda' (meaning 'the science of life'). Indians practiced vaccination as early as 550 BC.

Various other traditional systems of medicine were practiced in different parts of the world – like Homeopathy, Unani, Siddha system and Allopathy.

Allopathy means 'the other suffering'. This word still being used for the modern system of medicine, is a misnomer. Homoeopathy meaning 'similar suffering' was introduced by Hahnemann. The principles of this system include 'like cures like' and 'dilution enhances the potency of drugs'.

Thus several systems of medicine were introduced, of which only a few survived. The basic reason for the failure of many systems is that man's concepts about diseases were incorrect and baseless in those days. By the end of the 17th century the importance of experimentation, observation and scientific methods of study became clear. Francois Magendie and Claude Bernard popularised the use of animal experiments to understand the effects of drugs. Simultaneous development of other branches of science *viz*, botany, zoology, chemistry and physiology helped in the better understanding of pharmacology.

The last century has seen a rapid growth of the subject with several new drugs, new concepts and techniques being introduced. We now know much more about receptors and molecular mechanisms of action of many drugs. Several diseases, which were considered incurable and fatal, can now be completely cured with just a few tablets.

DEFINITIONS

The word pharmacology is derived from the Greek word—*Pharmacon* meaning an active principle and *logos* meaning a study (discourse).

Drug (*Droque*—a dry herb in French) is a substance used in the diagnosis, prevention or treatment of a disease. WHO definition—“A drug is any substance or product that is used or intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient.”

Pharmacodynamics is the study of the effects of the drugs on the body and their mechanisms of action, i.e. what the drug does to the body.

Pharmacokinetics is the study of the absorption, distribution, metabolism and excretion of drugs, i.e. what the body does to the drug (in Greek *Kinesis* = movement).

Therapeutics deals with the use of drugs in the prevention and treatment of disease.

Pharmacoeconomics deals with the cost, i.e. economic aspects of drugs used therapeutically.

Pharmacogenomics is a branch of pharmacogenetics which deals with the use of genetic information in selecting drugs for a person.

Pharmacoepidemiology is the study of both the useful and adverse effects of drugs on large numbers of people. *Pharmacovigilance* is a branch of pharmacoepidemiology which deals with the epidemiologic study of adverse drug effects.

Toxicology deals with the adverse effects of drugs and also the study of poisons, i.e. detection, prevention and treatment of poisonings (*Toxicon*=poison in Greek).

Chemotherapy is the use of chemicals for the treatment of infections. The term now also includes the use of chemical compounds to treat malignancies.

Pharmacopoeia (in Greek *Pharmacon* = drug; *poeia*=to make) is the official publication containing a list of drugs and medicinal

preparations approved for use, their formulae and other information needed to prepare a drug; their physical properties, tests for their identity, purity and potency. Each country may follow its own pharmacopoeia to guide its physicians and pharmacists. We thus have the Indian Pharmacopoeia (IP), the British Pharmacopoeia (BP) and the United States Pharmacopoeia (USP). The list is revised at regular periods to delete obsolete drugs and to include newly introduced ones.

Pharmacy is the science of identification, compounding and dispensing of drugs. It also includes collection, isolation, purification, synthesis and standardisation of medicinal substances.

SOURCES OF DRUGS

The sources of drugs could be *natural* or *synthetic*.

Natural sources Drugs can be obtained from:

1. *Plants*, e.g. atropine, morphine, quinine, and digoxin.
2. *Animals*, e.g. insulin, heparin, gonadotrophins and antitoxic sera.
3. *Minerals*, e.g. magnesium sulphate, aluminium hydroxide, iron, sulphur and radioactive isotopes.
4. *Microorganisms*—antibacterial agents are obtained from some bacteria and fungi. We thus have penicillin, cephalosporins, tetracyclines and other antibiotics.
5. *Human*—some drugs are obtained from human beings, e.g. immunoglobulins from blood, growth hormone from anterior pituitary and chorionic gonadotrophins from the urine of pregnant women.

Synthetic Most drugs used now are synthetic, e.g. quinolones, omeprazole, neostigmine, sulfonamides.

Many drugs are obtained by *cell cultures*, e.g. urokinase from cultured human kidney cells. Some are now produced by *recombinant DNA technology*, e.g. human insulin, tissue plasminogen activator, haematopoietic growth factors like erythropoietin and some others by *hybridoma technique* eg. monoclonal antibodies.

2

Routes of Drug Administration

Drugs may be administered by various routes. The choice of the route in a given patient depends on the properties of the drug and the patient's requirements. A knowledge of the advantages and disadvantages of the different routes of administration is essential.

The routes can be broadly divided into:

- Enteral
- Parenteral
- Local.

ENTERAL ROUTE (ORAL INGESTION)

Enteral route is the most commonly used, oldest and safest route of drug administration. The large surface area of the gastrointestinal tract, the mixing of its contents and the differences in pH at different parts of the gut facilitate effective absorption of the drugs given orally. However, the acid and enzymes secreted in the gut and the biochemical activity of the bacterial flora of the gut can destroy some drugs before they are absorbed.

Advantages

1. Safest route
2. Most convenient
3. Most economical
4. Drugs can be self-administered
5. Non-invasive route.

Disadvantages

1. Onset of action is slower as absorption needs time.

2. Irritant and unpalatable drugs cannot be administered.
3. Some drugs may not be absorbed due to certain physical and chemical characteristics, e.g. streptomycin is not effective orally.
4. Irritation to the gastrointestinal tract may lead to vomiting.
5. There may be irregularities in absorption.
6. Some drugs may be destroyed by gastric juices, e.g. insulin.
7. Oral preparations cannot be given to unconscious and uncooperative patients.
8. Some drugs may undergo extensive first pass metabolism in the liver.

To overcome some of the disadvantages, irritants are given in capsules, while bitter drugs are given as sugar coated tablets. Sometimes drugs are coated with substances like synthetic resins, gums, sugar, colouring and flavouring agents making them more acceptable.

Enteric Coated Tablets

Some tablets are coated with substances like cellulose-acetate, phthalate, gluten, etc. which are not digested by the gastric acid but get disintegrated in the alkaline juices of the intestine. This will:

- prevent gastric irritation.
- avoid destruction of the drug by the stomach.
- provide higher concentration of the drug in the small intestine.

- retard the absorption, and thereby prolong the duration of action.

But if the coating is inappropriate, the tablet may be expelled without being absorbed at all. Similarly controlled-release or sustained-release preparations are designed to prolong the rate of absorption and thereby the duration of action of drugs. This is useful for short-acting drugs. In newer controlled release formulations, the tablet is coated with a semipermeable membrane through which water enters and displaces the drug out.

Advantages

- Frequency of administration may be reduced.
- Therapeutic concentration may be maintained specially when nocturnal symptoms are to be treated.

Disadvantages

- There may be 'failure of the preparation' resulting in release of the entire amount of the drug in a short time, leading to toxicity.
- Enteric coated tablets are more expensive.

Certain precautions are to be taken during oral administration of drugs—capsules and tablets should be swallowed with a glass of water with the patient in upright posture either sitting or standing. This facilitates passage of the tablet into the stomach and its rapid dissolution. It also minimises chances of the drug getting into the larynx or behind the epiglottis. Recumbent patient should not be given drugs orally as some drugs may remain in the esophagus due to the absence of gravitational force facilitating the passage of the drug into the stomach. Such drugs can damage the esophageal mucosa, e.g. iron salts, tetracyclines.

Though enteral route mainly includes oral ingestion, sublingual and rectal administration may also be considered as enteral route.

PARENTERAL ROUTE

Routes of administration other than the enteral (intestinal) route are known as parenteral routes. Here the drugs are directly delivered into tissue fluids or blood.

Advantages

- Action is more rapid and predictable than oral administration.
- These routes can be employed in an unconscious or uncooperative patient.
- Gastric irritants can be given parenterally and therefore irritation to the gastrointestinal tract can be avoided.
- It can be used in patients with vomiting or those unable to swallow.
- Digestion by the gastric and intestinal juices and the first pass metabolism are avoided.

Therefore, in emergencies parenteral routes are very useful routes of drug administration as the action is rapid and predictable and are useful even in unconscious patients.

Disadvantages

- Asepsis must be maintained.
- Injections may be painful.
- More expensive, less safe and inconvenient.
- Injury to nerves and other tissues may occur.

Parenteral routes include :

1. Injections
2. Inhalation
3. Transdermal route
4. Transmucosal route.

INJECTIONS

Intradermal

The drug is injected into the layers of the skin raising a bleb, (e.g. BCG vaccine, tests for allergy) or by multiple punctures of the epidermis through a drop of the drug, e.g. smallpox vaccine. Only a small quantity can be administered by this route and it may be painful.

Subcutaneous (SC) Injection

Here the drug is deposited in the SC tissue, e.g. insulin, heparin. As this tissue is less vascular, absorption is slow and largely uniform making the drug long-acting. It is reliable and patients can be trained for self-administration. Absorption can be enhanced by the addition of the enzyme hyaluronidase.

Disadvantages

- As SC tissue is richly supplied by nerves, irritant drugs cannot be injected because they can cause severe pain.
- In shock, absorption is not dependable because of vasoconstriction.
- Repeated injections at the same site can cause lipoatrophy resulting in erratic absorption.

Hypodermoclysis is the SC administration of large volumes of saline employed in paediatric practice.

Drugs can also be administered subcutaneously as:

1. *Dermojet* In this method, a high velocity jet of drug solution is projected from a fine orifice using a gun. The solution gets deposited in the SC tissue from where it is absorbed. As needle is not required, this method is painless. It is suitable for vaccines.
2. *Pellet implantation* Small pellets packed with drugs are implanted subcutaneously.

The drug is slowly released for weeks or months to provide constant blood levels, e.g. testosterone, DOCA.

3. *Sialistic implants* The drug is packed in sialistic tubes and implanted subcutaneously. The drug gets absorbed over months to provide constant blood levels, e.g. hormones and contraceptives. The empty non-biodegradable implant has to be removed.

Intramuscular (IM)

Aqueous solution of the drug is injected into one of the large skeletal muscles—deltoid, triceps, gluteus or rectus femoris. Absorption into the plasma occurs by simple diffusion. Larger molecules enter through the lymphatic channels. As the muscles are vascular, absorption is rapid and quite uniform. Drugs are absorbed faster from the deltoid region than gluteal region especially in women. The volume of injection should not exceed 10 ml. For infants, rectus femoris is used instead of gluteus because gluteus is not well-developed till the child starts walking. If the drug is injected as an oily solution or suspension, absorption is slow and steady.

Advantages

- Intramuscular route is reliable.
- Absorption is rapid.
- Soluble substances, mild irritants, depot preparations, suspensions and colloids can be injected by this route.

Disadvantages

- Intramuscular injection may be painful and may even result in an abscess.
- Irritant solutions can damage the nerve if injected near a nerve. Nerve injury should be avoided.

Intravenous (IV)

Here, the drug is injected into one of the superficial veins so that it directly reaches the circulation and is immediately available for action.

Drugs can be given IV as:

1. A bolus—where an initial large dose is given, e.g. heparin. The drug is dissolved in a suitable amount of the vehicle and injected slowly.
2. Slow injection—over 15-20 minutes, e.g. aminophylline.
3. Slow infusion—when constant plasma concentrations are required, e.g. oxytocin in labour or when large volumes have to be given, e.g. dextrose, saline. Generally about one litre of solution is infused over 3 to 4 hours. However, the patient's condition and the drug factors like the onset and duration of action of the drug dictates the rate of infusion.

Advantages

- Most useful route in emergencies because the drug is immediately available for action.
- Provides predictable blood concentrations with 100% bioavailability.
- Large volumes of solutions can be given.
- Irritants can be given by this route as they get quickly diluted in blood.
- Rapid dose adjustments are possible—if unwanted effects occur, infusion can be stopped; if higher levels are required, infusion rate can be increased—specially for short-acting drugs.

Disadvantages

- Once injected, the drug cannot be withdrawn.
- Irritation of the veins may cause thrombophlebitis.
- Extravasation of some drugs may cause severe irritation and sloughing.

- Only aqueous solutions can be given IV but not suspensions, oily solutions and depot preparations.
- Self medication is difficult.

Intraperitoneal Peritoneum offers a large surface area for absorption. Fluids are injected intraperitoneally in infants. This route is also used for peritoneal dialysis.

Intrathecal Drugs can be injected into the subarachnoid space for action on the CNS, e.g. spinal anaesthetics. Some antibiotics and corticosteroids are also injected by this route to produce high local concentrations. Strict aseptic precautions are a must.

Drugs are also given **extradurally**. Morphine can be given **epidurally** to produce analgesia. Direct **intraventricular** administration of drugs may be employed in brain tumors.

Intra-articular Drugs are injected directly into a joint for the treatment of arthritis and other diseases of the joints, e.g. hydrocortisone is injected into the affected joint in rheumatoid arthritis. Strict aseptic precautions are required.

Intra-arterial Here drug is injected directly into the arteries. It is used only in the treatment of

- (i) peripheral vascular diseases,
- (ii) local malignancies
- (iii) diagnostic studies like angiograms.

Intramedullary Injection into a bone marrow—now rarely used.

INHALATION

Volatile liquids and gases are given by inhalation, e.g. general anaesthetics. In addition, drugs can be administered as solid particles, i.e. solutions of drugs can be atomised and the fine droplets are inhaled as aerosol, e.g. salbutamol. These inhaled drugs and vapours may act on the pulmonary epithelium and mucous membranes of the

respiratory tract and are also absorbed through these membranes.

Advantages

- Almost instantaneous absorption of the drug is achieved because of the large surface area of the lungs.
- In pulmonary diseases, it serves almost as a local route as the drug is delivered at the desired site making it more effective and less harmful.
- Hepatic first pass metabolism is avoided.
- Blood levels of volatile anaesthetics can be conveniently controlled as their absorption and excretion through the lungs are governed by the laws of gases.

Disadvantage

- Irritant gases may enhance pulmonary secretions—should be avoided. This is an important route of entry of certain drugs of abuse.

Transdermal

Highly lipid soluble drugs can be applied over the skin for slow and prolonged absorption, e.g. nitroglycerine ointment in angina pectoris. Adhesive units, inunction, iontophoresis and jet injection are some forms of transdermal drug delivery.

Adhesive units (transdermal therapeutic systems) are adhesive patches (Fig. 2.1) of different sizes and shapes made to suit the

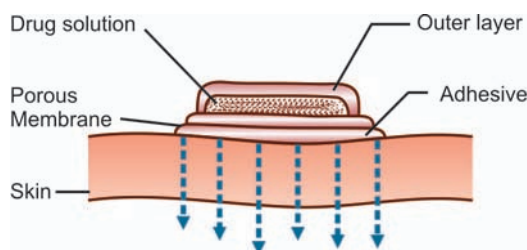


Fig. 2.1: Transdermal adhesive unit

area of application. The drug is held in a reservoir between an outer layer and a porous membrane. This membrane is smeared with an adhesive to hold on to the area of application. The drug slowly diffuses through the membrane and percutaneous absorption takes place. The rate of absorption is constant and predictable. Highly potent drugs (because small quantity is sufficient) and short acting drugs (because effect terminates quickly after the system is removed) are suitable for use in such systems.

Sites of application are chest, abdomen, upper arm, back mastoid region, and scrotum. Examples are hyoscine, nitroglycerine, testosterone, estrogen and fentanyl transdermal patches.

Advantages

- Duration of action is prolonged
- Provide constant plasma drug levels
- Patient compliance is good.

Inunction The route where a drug rubbed on to the skin gets absorbed to produce systemic effects is called inunction.

Iontophoresis In this procedure, galvanic current is used for bringing about penetration of lipid insoluble drugs into the deeper tissues where its action is required, e.g. salicylates. Fluoride iontophoresis is used in the treatment of dental hypersensitivity.

Jet injection As absorption of the drug occurs across the layers of the skin, dermojet may also be considered as a form of transdermal drug administration (description in page 5).

Transmucosal

Drugs are absorbed across the mucous membranes. Transmucosal administration includes sublingual, nasal and rectal routes. *Sublingual* Here, the tablet or pellet containing the drug is placed under the tongue. As the drug dissolves, it is absorbed

across the sublingual mucosa. The formulation should be lipid soluble, e.g. nitroglycerine, nifedipine, buprenorphine.

Advantages

- Absorption is rapid—within minutes the drug reaches the circulation.
- First pass metabolism is avoided.
- After the desired effect is obtained, the drug can be spat out to avoid the unwanted effects.

Disadvantages

- Buccal ulceration can occur.
- Lipid insoluble drugs cannot be given.

Nasal Drugs can be administered through nasal route either for systemic absorption or for local effects.

E.g.

- (a) for systemic absorption—oxytocin spray
- (b) for local effect—decongestant nasal drops, e.g. oxymetazoline; budesonide nasal spray for allergic rhinitis.

Rectal Rectum has a rich blood supply and drugs can cross the rectal mucosa to be absorbed for systemic effects. Drugs absorbed from the upper part of the rectum are carried by the superior haemorrhoidal veins to the portal circulation (can undergo first pass metabolism), while that absorbed from the lower part of the rectum is carried by the middle and inferior haemorrhoidal veins to the systemic circulation. Drugs like indomethacin, chlorpromazine, diazepam and paraldehyde can be given rectally.

Some irritant drugs are given rectally as *suppositories* because they cannot be given orally.

Advantages

- Gastric irritation is avoided.
- Can be administered by unskilled persons.
- Useful in geriatric patients; patients with vomiting and those unable to swallow.

Disadvantages

- Irritation of the rectum can occur.
- Absorption may be irregular and unpredictable.

Drugs may also be given by rectal route as *enema*.

Enema is the administration of a drug in a liquid form into the rectum. Enema may be evacuant or retention enema.

Evacuant enema In order to empty the bowel, about 600 ml of soap water is administered per rectum. Water distends and thus stimulates the rectum while soap lubricates. Enema is given prior to surgeries, obstetric procedures and radiological examination of the gut.

Retention enema The drug is administered with about 100 ml of fluids and is retained in the rectum for local action, e.g. prednisolone enema in ulcerative colitis.

TOPICAL

Drugs may be applied on the skin for local action as ointment, cream, gel, powder, paste, etc. Drugs may also be applied on the mucous membrane as in the eyes, ears and nose as ointment, drops and sprays. Drugs may be administered as *suppository* for rectum, *bougie* for urethra and *pessary* and *douche* for vagina. Pessaries are oval shaped tablets to be placed in the vagina to provide high local concentrations of the drug at the site, e.g. antifungal pessaries in vaginal candidiasis.

SPECIAL DRUG DELIVERY SYSTEMS

In order to improve drug delivery, to prolong the duration of action and thereby improve patient compliance, special drug delivery systems are being tried. Drug targeting, i.e. to deliver drugs at the site where it is required to act is also being aimed at, especially for anticancer drugs. Some such

systems are ocuserts, progestaserts, transdermal adhesive units, prodrugs, osmotic pumps, computerised pumps and methods using monoclonal antibodies and liposomes as carriers.

Ocusert Ocusert systems are thin elliptical units that contain the drug in a reservoir which slowly releases the drug through a membrane by diffusion at a steady rate, e.g. pilocarpine ocusert used in glaucoma is placed under the lid and can deliver pilocarpine for 7 days.

Progestasert is inserted into the uterus where it delivers progesterone constantly for over one year.

Transdermal adhesive units See page 7.

Prodrug is an inactive form of a drug which gets metabolised to the active derivative in the body. A prodrug may overcome some of the disadvantages of the conventional forms of drug administration, e.g. dopamine does not cross the BBB; levodopa, a prodrug crosses the BBB and is then converted to dopamine in the CNS. Prodrugs may also be used to achieve longer duration of action, e.g. Bacampicillin (a prodrug of ampicillin) is longer acting than ampicillin. Cyclophosphamide - an anticancer drug - gets converted to its active metabolite aldophosphamide in the liver. This allows oral administration of cyclophosphamide without causing much gastrointestinal toxicity. Zidovudine is taken up by virus infected cells and gets activated in these cells. This results in selective toxicity to infected cells. A prodrug may be more stable at gastric

pH, e.g. aspirin is converted to salicylic acid which is the active drug and aspirin is better tolerated than salicylic acid.

Osmotic pumps - are small tablet shaped units containing the drug and an osmotic substance in two different chambers. The tablet is coated with a semipermeable membrane in which a minute laser-drilled hole is made. When the tablet is swallowed and reaches the gut, water enters into the tablet through the semipermeable membrane. The osmotic layer swells and pushes the drug slowly out of the laser-drilled orifice. This allows slow and constant delivery of the drug over a long period of time. It is also called Gastrointestinal Therapeutic System (GITS). Some drugs available in this formulation are iron and prazosin.

Computerised miniature pumps These are programmed to release drugs at a definite rate either continuously as in case of insulin or intermittently in pulses as in case of GnRH.

Various methods of drug targeting are tried especially for anticancer drugs to reduce toxicity.

Monoclonal antibodies against the tumor specific antigens are used to deliver anticancer drugs to specific tumor cells.

Liposomes are phospholipids suspended in aqueous vehicles to form minute vesicles. Drugs encapsulated in liposomes are taken up mainly by the reticuloendothelial cells of the liver and are also concentrated in malignant tumors. Thus site-specific delivery of drugs may be possible with the help of liposomes.

3

Pharmacokinetics

Pharmacokinetics is the study of the absorption, distribution, metabolism and excretion of drugs, i.e. the movement of the drugs into, within and out of the body. For a drug to produce its specific response, it should be present in adequate concentrations at the site of action. This depends on various factors apart from the dose. Once the drug is administered, it is absorbed, i.e. enters the blood, is distributed to different parts of the body, reaches the site of action, is metabolised and excreted (Fig. 3.1). All these processes involve passage of the drug molecules across various barriers—like the intestinal epithelium, cell membrane, renal filtering membrane, capillary barrier and so on. To cross these barriers the drug has to cross the cell membrane or pass in-between the epithelial or endothelial cells.

The cell membrane/biological membrane is made up of two layers of phospholipids with intermingled protein molecules (Fig. 3.2). All lipid soluble substances get dissolved in the cell membrane and readily permeate into the cells. The junctions between adjacent epithelial or endothelial cells have pores through which small water-soluble

molecules can pass. Movement of some specific substances is regulated by special carrier proteins. The passage of drugs across biological membranes involves processes like passive (filtration, diffusion) and active transport.

Mechanisms of Transport of Drugs Across Biological Membranes

Passive transfer

- Simple diffusion
- Filtration

Carrier-mediated transport

- Active transport
- Facilitated diffusion

Endocytosis

Passive Transfer

The drug moves across a membrane without any need for energy.

Simple diffusion is the transfer of a drug across the membrane in the direction of its concentration gradient. Lipid soluble drugs are transferred across membranes by simple diffusion—after dissolving in the lipids of the cell membrane.

Filtration is the passage of drugs through aqueous pores in the membrane. Water-soluble drugs with molecular size smaller than the diameter of the pores cross the biological membranes by filtration.

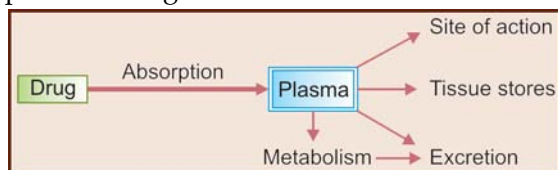


Fig. 3.1: Schematic representation of movement of drug in the body

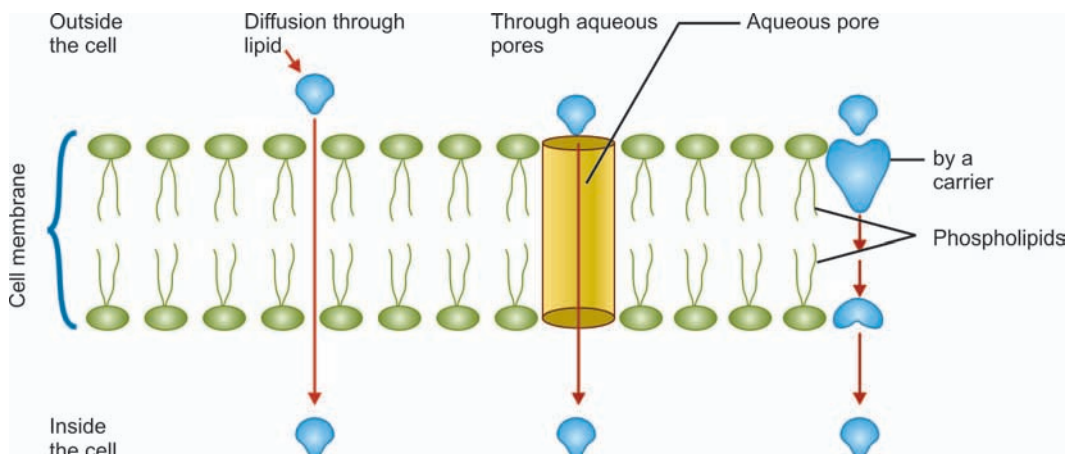


Fig. 3.2: Movement of drugs across biological membrane

Carrier-mediated Transport

Active transport is the transfer of drugs against a concentration gradient and needs energy. It is carried by a specific carrier protein. Only drugs related to natural metabolites are transported by this process, e.g. levodopa, iron, amino acids. The compound binds to a specific carrier on one side of the membrane and moves across the cell. At the other side of the cell, the complex dissociates and the carrier moves back to transport another molecule. Other substances competing for the same mechanism for transport may interfere with drug movement as this process is saturable, e.g. penicillin and probenecid - duration of action of penicillin is prolonged because both of them compete for renal tubular secretion.

Facilitated diffusion is a unique form of carrier transport which differs from active transport in that it is not energy dependent and the movement occurs in the direction of the concentration gradient. The carrier facilitates diffusion and is highly specific for the

substance, e.g. uptake of glucose by cells, vitamin B₁₂ from intestines.

Endocytosis

Endocytosis is the process where small droplets are engulfed by the cell. Some proteins are taken up by this process (like pinocytosis in amoeba). This process is currently being tried for delivery of some anticancer drugs to the tissues. The reverse process— exocytosis is responsible for secretion of many substances from cells, e.g. neurotransmitters stored in nerve endings.

ABSORPTION

Absorption is defined as the passage of the drug from the site of administration into the circulation. For a drug to reach its site of action, it must pass through various membranes depending on the route of administration. Absorption occurs by one of the processes described above, i.e. passive diffusion or carrier-mediated transport. Thus except for intravenous route, absorption is

important for all other routes of administration. Several factors influence the rate and extent of absorption of a drug (Fig. 3.3). They are:

1. *Disintegration and dissolution time* The drug taken orally should break up into individual particles (disintegrate) to be absorbed. It then has to dissolve in the gastrointestinal fluids. In case of drugs given subcutaneously or intramuscularly,
2. *Formulation* Pharmaceutical preparations are formulated to produce desired absorption. Inert substances used with drugs as diluents like starch and lactose

the drug molecules have to dissolve in the tissue fluids. Liquids are absorbed faster than solids. Delay in disintegration and dissolution as with poorly water-soluble drugs like aspirin, results in delayed absorption.

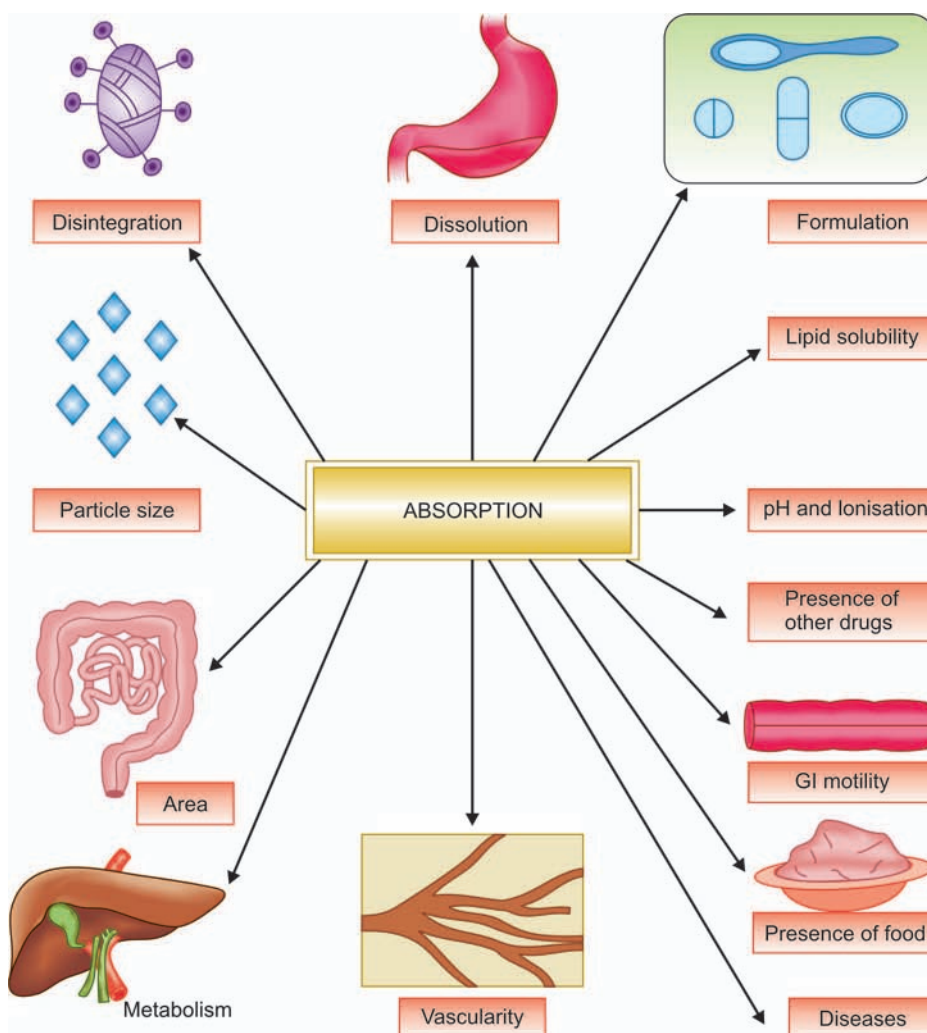


Fig. 3.3: Factors affecting absorption of drugs

may sometimes interfere with absorption.

3. **Particle size** Small particle size is important for better absorption of drugs. Drugs like corticosteroids, griseofulvin, digoxin, aspirin and tolbutamide are better absorbed when given as small particles. On the other hand, when a drug has to act on the gut and its absorption is not desired, then particle size should be kept large, e.g. anthelmintics like bephenium hydroxynaphthoate.
4. **Lipid solubility** Lipid soluble drugs are absorbed faster and better by dissolving in the phospholipids of the cell membrane.
5. **pH and ionisation** Ionised drugs are poorly absorbed while unionised drugs are lipid soluble and are well absorbed. Most drugs are weak electrolytes and exist in both ionized and unionized forms. But the degree of ionisation depends on the pH. Thus acidic drugs remain unionised in the acidic medium of the stomach and are rapidly absorbed from the stomach, e.g. aspirin, barbiturates. Basic drugs are unionised when they reach the alkaline medium of the intestine from where they are rapidly absorbed, e.g. pethidine, ephedrine.

Strong acids and bases are highly ionised and therefore poorly absorbed, e.g. heparin, streptomycin.

6. **Area and vascularity of the absorbing surface** The larger the area of absorbing surface and more the vascularity—better is the absorption. Thus most drugs are absorbed from the small intestine.
7. **Gastrointestinal motility**

Gastric emptying time—if gastric emptying is faster, the passage of the drug to the intestines is quicker and hence absorption is faster.

Intestinal motility—when highly increased as in diarrhoeas, drug absorption is reduced.

8. **Presence of food** delays gastric emptying, dilutes the drug and delays absorption. Drugs may form complexes with food constituents and such complexes are poorly absorbed, e.g. tetracyclines chelate calcium present in the food because of which their bioavailability is decreased. Moreover, certain drugs like ampicillin, roxithromycin and rifampicin are well absorbed only on empty stomach.
9. **Metabolism** Some drugs may be degraded in the GI tract, e.g. nitroglycerine, insulin. Such drugs should be given in higher doses or by alternative routes.
10. **Diseases of the gut** like malabsorption and achlorhydria result in reduced absorption of drugs.

First pass metabolism is the metabolism of a drug during its passage from the site of absorption to the systemic circulation. It is also called presystemic metabolism or first pass effect and is an important feature of oral route of administration. Drugs given orally may be metabolised in the gut wall and in the liver before reaching the systemic circulation. The extent of first pass metabolism differs from drug to drug and among individuals from partial to total

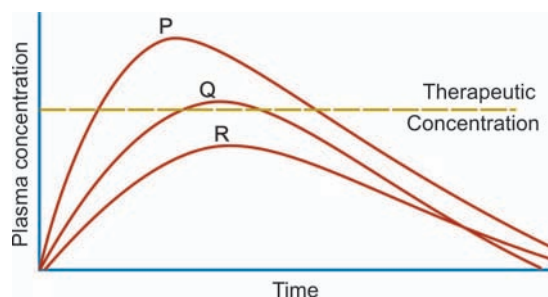


Fig. 3.4: Study of bioequivalence. Three different oral formulations-P, Q & R of the same drug yield different bioavailability values

inactivation. When it is partial, it can be compensated by giving higher dose of the particular drug, e.g. nitroglycerine, propranolol, salbutamol. But for drugs that undergo complete first pass metabolism, the route of administration has to be changed, e.g. isoprenaline, hydrocortisone, insulin. Bioavailability of many drugs is increased in patients with liver disease due to reduction in hepatic metabolism.

First Pass Metabolism

- is metabolism of a drug during its first passage through gut wall and liver
- reduces bioavailability
- extent of metabolism depends on the drug and individuals
- measures to compensate first pass effect
 - dose has to be increased for some drugs like propranolol
 - route has to be changed for some others like hydrocortisone
- Examples: morphine, chlorpromazine, nitroglycerine, verapamil, testosterone, insulin, lignocaine.

Bioavailability

Bioavailability is the fraction of the drug that reaches the systemic circulation following administration by any route. Thus for a drug given intravenously, the bioavailability is 100%. On IM/SC injection, drugs are almost completely absorbed while by oral route, bioavailability may be low due to incomplete absorption and first pass metabolism. For example bioavailability of chlortetracycline is 30%, carbamazepine 70%, chloroquine 80%, minocycline and diazepam 100%. Transdermal preparations are absorbed systemically and may have 80-100% bioavailability. Infact all the ten factors which influence the absorption of a drug also alter

the bioavailability. Large bioavailability variations of a drug particularly when it is unpredictable can result in toxicity or therapeutic failure as in case of halofantrine.

Bioequivalence

Comparison of bioavailability of different formulations of the same drug is the study of bioequivalence. Often oral formulations containing the same amount of a drug from different manufacturers may result in different plasma concentrations, i.e. there is no bioequivalence among them (Fig. 3.4.) Such differences occur with poorly soluble, slowly absorbed drugs mainly due to differences in the rate of disintegration and dissolution. Variations in bioavailability (nonequivalence) can result in toxicity or therapeutic failure in drugs that have low safety margin like digoxin and drugs that need precise dose adjustment like anticoagulants and corticosteroids. For such drugs, in a given patient, the preparations from a single manufacturer should be used.

DISTRIBUTION

After a drug reaches the systemic circulation, it gets distributed to other tissues. It should cross several barriers before reaching the site of action. Like absorption, distribution also involves the same processes, i.e. filtration, diffusion and specialised transport. Various factors determine the rate and extent of distribution, *viz* lipid solubility, ionisation, blood flow and binding to plasma proteins and cellular proteins. Unionised lipid soluble drugs are widely distributed throughout the body.

Plasma Protein Binding

On reaching the circulation most drugs bind to plasma proteins; acidic drugs bind mainly albumin and basic drugs to alpha-acid

Table 3.1: Some highly protein bound drugs

Warfarin	Tolbutamide	Phenytoin
Frusemide	Clofibrate	Sulfonamides
Diazepam	Salicylates	Phenylbutazone
Indomethacin		

glycoprotein. The free or unbound fraction of the drug is the only form available for action, metabolism and excretion while the protein bound form serves as a reservoir. The extent of protein binding varies with each drug, e.g. warfarin is 99% and morphine is 35% protein bound while binding of ethosuximide and lithium is 0%, i.e. they are totally free (Table 3.1).

Clinical Significance of Plasma Protein Binding

1. Only free fraction is available for action, metabolism and excretion. When the free drug levels in the plasma fall, bound drug is released.
2. Protein binding serves as a store (reservoir) of the drug and the drug is released when free drug levels fall.
3. Protein binding prolongs the duration of action of the drug.
4. Many drugs may compete for the same binding sites. Thus one drug may displace another from the binding sites and result in displacement interactions, e.g. warfarin is 99% protein bound (i.e. free fraction is 1%). If another drug like indomethacin reduces its binding to 95%, the free form then becomes 5% which means, there is a 5-fold increase in free warfarin levels which could result in toxicity. Fortunately the body largely compensates by enhancing metabolism and excretion.
5. Chronic renal failure and chronic liver disease result in hypoalbuminaemia with reduced protein binding of drugs. Highly protein bound drugs should be carefully used in such patients.

Tissue binding Some drugs get bound to certain tissue constituents because of special affinity for them. Tissue binding delays elimination and thus prolongs the duration of action of the drug. For example, lipid soluble drugs are bound to adipose tissue. Tissue binding also serves as a reservoir of the drug.

<i>Tissue</i>	<i>Binding drugs</i>
Adipose tissue	Thiopentone sodium, benzodiazepines
Muscles	Emetine
Bone	Tetracyclines, Lead
Retina	Chloroquine
Thyroid	Iodine

Redistribution When some highly lipid soluble drugs are given intravenously or by inhalation, they get rapidly distributed into highly perfused tissues like brain, heart and kidney. But soon they get redistributed into less vascular tissues like the muscle and fat resulting in termination of the action of these drugs. The best example is the intravenous anaesthetic thiopental sodium which induces anaesthesia in 10-20 seconds but the effect ceases in 5-15 minutes due to redistribution.

Blood-brain barrier (BBB) The endothelial cells of the brain capillaries lack intercellular pores and instead have tight junctions. Moreover, glial cells envelop the capillaries and together these form the BBB. Only lipid soluble, unionised drugs can cross this BBB. During inflammation of the meninges, the barrier becomes more permeable to drugs, e.g. penicillin readily penetrates during meningitis. The barrier is weak at some areas like the CTZ, posterior pituitary and parts of hypothalamus and allows some compounds to diffuse.

Placental barrier Lipid soluble, unionised drugs readily cross the placenta while lipid insoluble drugs cross to a much lesser extent.

Thus drugs taken by the mother can cause several unwanted effects in the foetus (Table 3.5)

Volume of Distribution (V_d)

For the purpose of pharmacokinetic studies, body can be considered as a single compartment into which drugs are distributed uniformly. Each drug actually follows its own pattern of distribution from plasma to other body fluids and tissues.

Apparent volume of distribution is defined as the volume necessary to accommodate the entire amount of the drug administered, if the concentration throughout the body were equal to that in plasma. It relates the amount of the drug in the body to the concentration of the drug in plasma. It is calculated as

$$V_d = \frac{\text{Amount of drug in the body}}{\text{Plasma concentration}}$$

For example, if the dose of a drug given is 500 mg and it attains a uniform concentration of 10 mg/litre of the plasma, its $V_d = 50$ litres. Important facts about V_d are:

- If a drug is retained mostly in the plasma, its V_d is small (e.g. aspirin, aminoglycosides) while if it is distributed widely in other tissues then its V_d is large (e.g. pethidine)
- The knowledge of V_d of drugs is clinically important in the treatment of poisoning. Drugs with large V_d like pethidine are not easily removed by haemodialysis because such drugs are widely distributed in the body.

- V_d may vary with changes in tissue permeability and protein binding as seen in some diseases.
- Drugs extensively bound to plasma proteins have a low V_d - e.g. phenylbutazone.

BIOTRANSFORMATION (METABOLISM)

Biotransformation is the process of biochemical alteration of the drug in the body. Body treats most drugs as foreign substances and tries to inactivate and eliminate them by various biochemical reactions. These processes convert the drugs into more polar, water-soluble compounds so that they are easily excreted through the kidneys. Some drugs may be excreted largely unchanged in the urine, e.g. frusemide, atenolol.

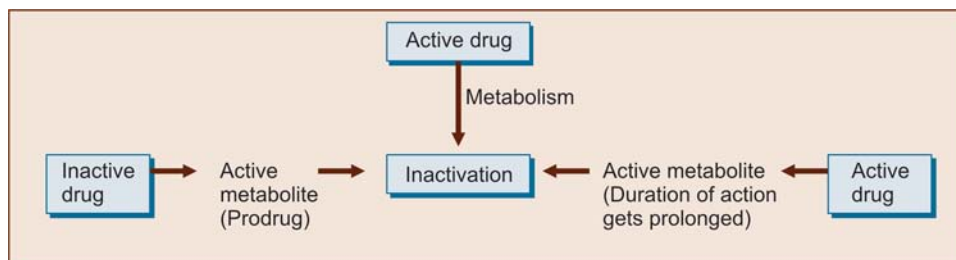
Site The most important organ of biotransformation is the liver. But drugs are also metabolised by the kidney, gut, mucosa, lungs, blood and skin.

Consequences of biotransformation Though biotransformation generally inactivates the drug, some drugs may be converted to metabolites which are also active or more active than the parent drug. Biotransformation may also activate an inactive drug (Table 3.2). When the metabolite is active, the duration of action gets prolonged (Table 3.3). Prodrug is an inactive drug which gets converted into an active form in the body. In case of some drugs, the active metabolite may be toxic. For example: paracetamol is converted to n-acetyl-p-benzo-

Table 3.2: Consequences of biotransformation

Active drug to inactive metabolite	Active drug to active metabolite	Inactive drug to active metabolite (prodrug)
e.g. Morphine Chloramphenicol	e.g. Primidone ▶ Phenobarbitone Digitoxin ▶ Digoxin Diazepam ▶ Oxazepam	e.g. Levodopa ▶ Dopamine Prednisone ▶ Prednisolone Enalapril ▶ Enalaprilat

Table 3.3: Biotransformation



quinoneimine which causes hepatotoxicity; cyclophosphamide is converted to acrolein which causes bladder toxicity.

Enzymes in biotransformation The biotransformation reactions are catalysed by specific enzymes located either in the liver microsomes (microsomal enzymes) or in the cytoplasm and mitochondria of the liver cells and also in the plasma and other tissues (non-microsomal enzymes).

The chemical reactions of biotransformation can take place in two phases (Fig. 3.5).

1. Phase I (Non-synthetic reactions)
2. Phase II (Synthetic reactions).

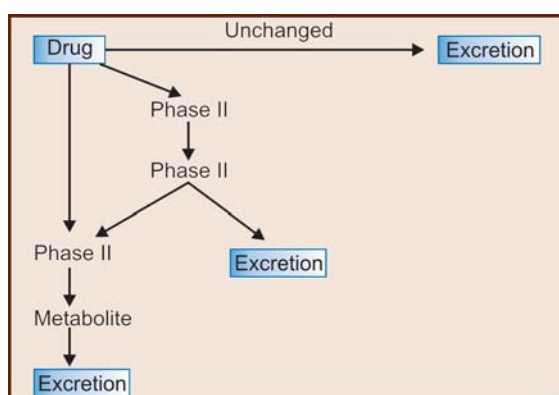


Fig. 3.5: Phases in metabolism of drugs. A drug may be excreted as phase I metabolite or as phase II metabolite. Some drugs may be excreted as such

Phase I reactions convert the drug to a more polar metabolite by oxidation, reduction or hydrolysis. Oxidation reactions are the most important metabolising reactions, mostly catalysed by mono-oxygenases present in the liver (Table 3.4). If the metabolite is not sufficiently polar to be excreted, it undergoes phase II reactions.

Phase II reactions In phase II reactions, endogenous water-soluble substances like glucuronic acid, sulfuric acid, glutathione or an amino acid combine with the drug or its phase I metabolite to form a highly polar conjugate which is inactive and gets readily excreted by the kidneys. Large molecules are excreted through the bile.

Conjugation results invariably in inactivation of the drug. Some products of conjugation are glucuronides, ethereal sulfates and amino acid conjugates. Glucuronide conjugation is the most common type of metabolic reaction. Endogenous substances like bilirubin and steroid hormones also undergo conjugation. Drugs like sulfonamides and isoniazid undergo conjugation with acetylcoenzyme A (acetylation) while some like adrenaline undergo methylation. Glutathione conjugation inactivates highly reactive intermediates formed during the metabolism of drugs like paracetamol.

Table 3.4: Important drug biotransformation reactions

Reactions	Examples of drugs
Oxidation	Phenytoin, Diazepam, Ibuprofen, Amphetamine, Chlorpromazine, Dapsone
Reduction	Chloramphenicol, Halothane
Hydrolysis	Pethidine, Procaine
<i>Conjugation reactions</i>	
Glucuronide conjugation	Chloramphenicol, Morphine
Acetylation	Sulfonamides, Isoniazid
Methylation	Adrenaline, Histamine
Glutathione conjugation	Paracetamol

ENZYME INDUCTION

Microsomal enzymes are located in the microsomes that line the smooth endoplasmic reticulum of the liver cells. The synthesis of these enzymes, mainly cytochrome P450 can be enhanced by certain drugs and environmental pollutants. This is called *enzyme induction* and this process speeds up the biotransformation of the inducing drug itself and other drugs metabolised by the microsomal enzymes, e.g. phenobarbitone, rifampicin, alcohol, cigarette smoke, DDT, griseofulvin, carbamazepine and phenytoin are some enzyme inducers.

Clinical relevance of microsomal enzyme induction:

1. Drug interactions

- Therapeutic failure - By speeding up metabolism, enzyme induction may reduce the duration of action of some other drugs which can result in therapeutic failure, e.g. failure of oral contraceptives in patients taking rifampicin.
- Toxicity - Enzyme induction may result in toxicity due to production of higher amounts of the toxic intermediate metabolites, e.g. a patient undergoing treatment with rifampicin is likely to develop hepatotoxicity with paracetamol because a higher amount of the

toxic intermediate metabolite of paracetamol is formed due to enzyme induction.

- Tolerance to drugs may develop* as in case of carbamazepine since it induces its own metabolism called autoinduction.
- Result in disease*—antiepileptics enhance the breakdown of vitamin D resulting in osteomalacia on long-term administration.
- Variable response* In chronic smokers and alcoholics, enzyme induction may result in failure to achieve the expected response to some drugs metabolised by the same enzymes.
- Therapeutic application of enzyme induction* Neonates are deficient in both microsomal and non-microsomal enzymes. Hence their capacity to conjugate bilirubin is low which results in jaundice. Administration of phenobarbitone - an enzyme inducer, helps in rapid clearance of the jaundice in them by enhancing bilirubin conjugation.

Enzyme inhibition Some drugs inhibit cytochrome P450 enzyme activity. Drugs like cimetidine and ketoconazole bind to cytochrome P450 and thus competitively inhibit the metabolism of endogenous substances like testosterone and other drugs given concurrently. Enzyme inhibition by drugs is the basis of several drug interactions.

Chloramphenicol, erythromycin, ketconazole, cimetidine, ciprofloxacin and verapamil are some enzyme inhibitors.

Factors that Influence Biotransformation

Genetic variation results in altered metabolism of drugs, e.g. succinylcholine is metabolised very slowly in people with defective pseudocholinesterase resulting in prolonged apnoea.

Environmental pollutants like cigarette smoke cause enzyme induction.

Age At extremes of age, the activity of metabolic enzymes in the liver is low and hence there is increased risk of toxicity with drugs.

Diseases of the liver markedly affect metabolism of drugs.

Drugs are excreted from the body after being converted to water-soluble metabolites while some are directly eliminated without metabolism. The major organs of excretion are the kidneys, the intestine, the biliary system and the lungs. Drugs are also excreted in small amounts in the saliva, sweat and milk.

EXCRETION

Renal Excretion

Kidney is the most important organ of drug excretion. The three processes involved in the elimination of drugs through kidneys are glomerular filtration, active tubular secretion and passive tubular reabsorption.

Glomerular filtration The rate of filtration through the glomerulus depends on GFR, concentration of free drug in the plasma and its molecular weight. Ionised drugs of low molecular weight (< 10,000) are easily filtered through the glomerular membrane.

Active tubular secretion Cells of the proximal tubules actively secrete acids and bases by two transport systems. Thus acids like

penicillin, salicylic acid, probenecid, frusemide and bases like amphetamine and histamine are so excreted. Drugs may compete for the same transport system resulting in prolongation of action of each other, e.g. penicillin and probenecid.

Passive tubular reabsorption Passive diffusion of drug molecules can occur in either direction in the renal tubules depending on the drug concentration, lipid solubility and pH. As highly lipid soluble drugs are largely reabsorbed, their excretion is slow. Acidic drugs get ionised in alkaline urine and are easily excreted while bases are excreted faster in acidic urine. This property is useful in the treatment of poisoning. In poisoning with acidic drugs like salicylates and barbiturates, forced alkaline diuresis (Diuretic + sodium bicarbonate + IV fluids) is employed to hasten drug excretion. Similarly, elimination of basic drugs like quinine and amphetamine is enhanced by forced acid diuresis.

Faecal and Biliary Excretion

Unabsorbed portion of the orally administered drugs are eliminated through the faeces. Liver transfers acids, bases and unionised molecules into bile by specific acid transport processes. Large water-soluble conjugates are excreted in the bile. Some drugs may get reabsorbed in the lower portion of the gut and are carried back to the liver. Such recycling is called *enterohepatic circulation* and it prolongs the duration of action of the drug; examples are chloramphenicol, tetracycline, oral contraceptives and erythromycin.

Pulmonary Excretion

The lungs are the main route of elimination for gases and volatile liquids *viz.* general anaesthetics and alcohol. This also has legal implications in medicolegal practice.

Other Routes of Excretion

Small amounts of some drugs are eliminated through the **sweat** and **saliva**. Excretion in saliva may result in a unique taste with some drugs like phenytoin, clarithromycin; metallic taste with metronidazole, metoclopramide and disulfiram. Drugs like iodide, rifampicin and heavy metals are excreted through sweat.

The excretion of drugs in the **milk** is in small amounts and is of no significance to the mother. But, for the suckling infant, it may be sometimes important especially because of the infant's immature metabolic and excretory mechanisms. Though most drugs can be taken by the mother without significant toxicity to the child, there are a few exceptions (Table 3.5).

CLINICAL PHARMACOKINETICS

The knowledge of pharmacokinetics is clinically useful for several purposes including selection and adjustment of the dosage regimen, and to obtain optimum effects from a drug. The three most important pharmacokinetic parameters are **bioavailability** (page 14), **volume of distribution** (page 16) and **clearance**.

Clearance (CL) is the volume of plasma freed completely of the drug in unit time. It can be calculated by the ratio of the rate of elimination to the plasma concentration.

$$\text{Thus, CL} = \frac{\text{Rate of elimination}}{\text{Plasma concentration}}$$

Clearance is expressed as ml/litre/unit time.

Clearance is the most important factor determining drug concentration and should be considered when any drug is intended for long-term administration.

Drugs are metabolised/eliminated from the body by:

Table 3.5: Example of drugs that could be toxic to the suckling infant when taken by the mother

Sulphasalazine	Doxepin
Theophylline	Amiodarone
Anticancer drugs	Primidone
Salicylates	Ethosuximide
Chloramphenicol	Phenobarbitone
Nalidixic acid	Phenothiazines
Nitrofurantoin	β-blockers

1. *First-order kinetics* In first order kinetics, a constant *fraction* of the drug is metabolised/eliminated per unit time. Most drugs follow first order kinetics and the rate of metabolism/excretion is dependent on their concentration (exponential) in the body (Fig. 3.6). It also holds good for absorption of drugs.
2. *Zero order kinetics (Saturation kinetics)* Here a constant *amount* of the drug present in the body is metabolised/eliminated per unit time. The metabolic enzymes get saturated and hence with increase in dose, the plasma drug level increases disproportionately resulting in toxicity.

Some drugs like phenytoin and warfarin are eliminated by both processes, i.e. by first order initially and by zero order at higher concentrations.

Example of drugs that follow zero order kinetics:

- Alcohol
- Phenytoin
- Aspirin
- Heparin
- Phenylbutazone.

Plasma Half-life and Steady State Concentration

Plasma half-life ($t_{1/2}$) is the time taken for the plasma concentration of a drug to be reduced to half its value (Fig. 3.7). Four to five half-lives are required for the complete elimination of a drug. Each drug has its own

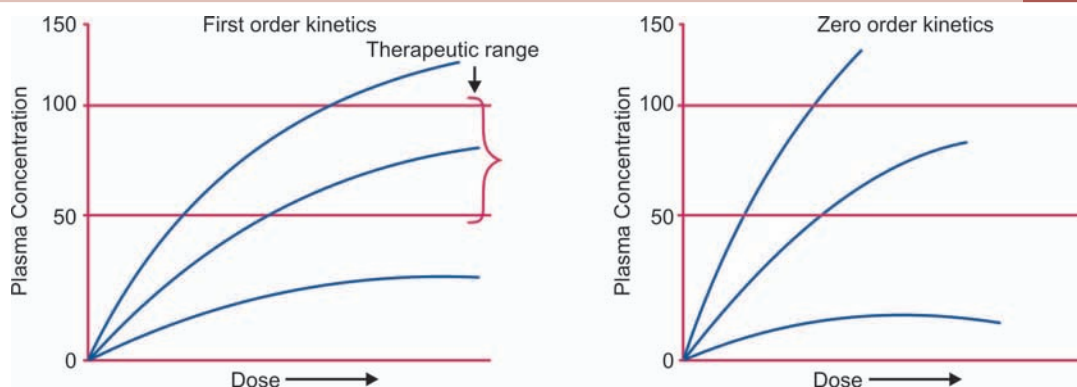


Fig. 3.6: First order kinetics-As the plasma concentration rises, metabolism and excretion proportionately increase. **Zero order kinetics**-In higher doses, the drug accumulates and the plasma concentration rises resulting in toxicity

$t_{1/2}$ and is an important pharmacokinetic parameter that guides the dosing regimen. It helps in calculating loading and maintenance doses of a drug. It also indicates the duration of action of a drug.

Biological half-life is the time required for total amount of the drug in the body to be reduced to half.

Biological effect half-life is the time required for the biological effect of the drug to reduce to half. With some drugs like propranolol the pharmacological effect of the drug may last much longer, i.e. even after its plasma levels fall. In such drugs, biological effect half life gives an idea of the duration of action of the drug.

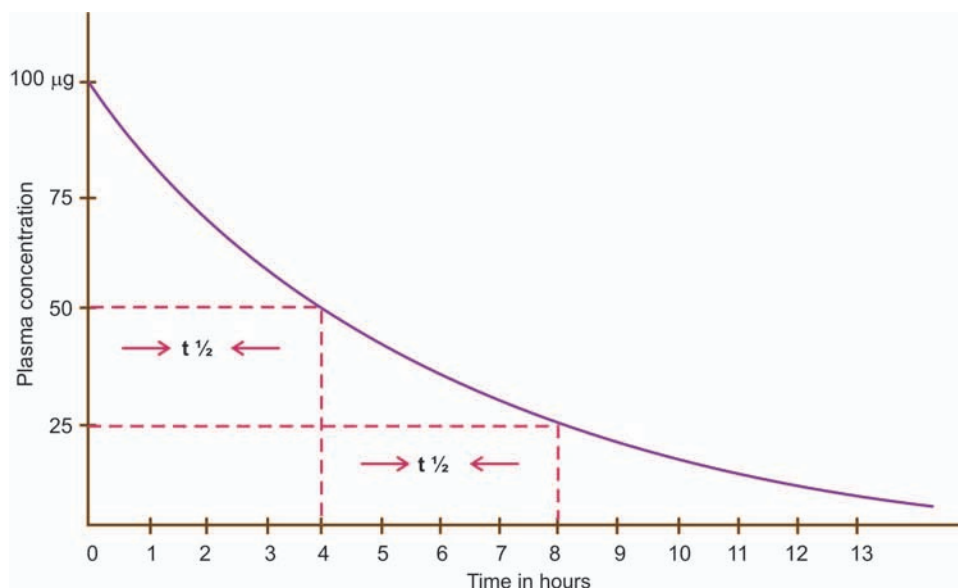


Fig. 3.7: Plasma half life

If a drug is administered repeatedly at short intervals before complete elimination, the drug accumulates in the body and reaches a 'state' at which the rate of elimination equals the rate of administration. This is known as the '*Steady-state*' or plateau level (Fig. 3.8). After attaining this level, the plasma concentration fluctuates around an average steady level. It takes 4-5 half-lives for the plasma concentration to reach the plateau level.

DRUG DOSAGE

Depending on the patient's requirements and the characteristics of the drug, drug dosage can be of the following kinds -

Fixed dose In case of reasonably safe drugs, a fixed dose of the drug is suitable for most patients, e.g. analgesics like paracetamol—500 mg to 1000 mg 6 hourly is the usual adult dose.

Individualised dose For some drugs especially the ones with low safety margin, the dose has to be 'tailored' to the needs of each patient, e.g. anticonvulsants, antiarrhythmic drugs.

Loading dose In situations when target plasma concentrations have to be attained rapidly, a loading/bolus dose of the drug is given at

the beginning of the treatment. A loading dose is a single large dose or a series of quickly repeated doses given to rapidly attain target concentration, e.g. heparin given as 5000 IU bolus dose. Once the target level is reached, a *maintenance dose* is sufficient to 'maintain the drug level' and to balance the elimination.

The disadvantage with the loading dose is that the patient is rapidly exposed to high concentrations of the drug which may result in toxicity.

Therapeutic drug monitoring The response to a drug depends on the plasma concentration attained in the patient. This in turn depends on the bioavailability, volume of distribution and clearance. As these parameters vary among individuals, there is a wide variation in the plasma concentration attained from patient to patient. Hence in some situations it may be necessary to monitor treatment by measuring plasma drug concentrations. Such situations are:

1. while using drugs with low safety margin—to avoid therapeutic failure, e.g. digoxin, theophylline, lithium.

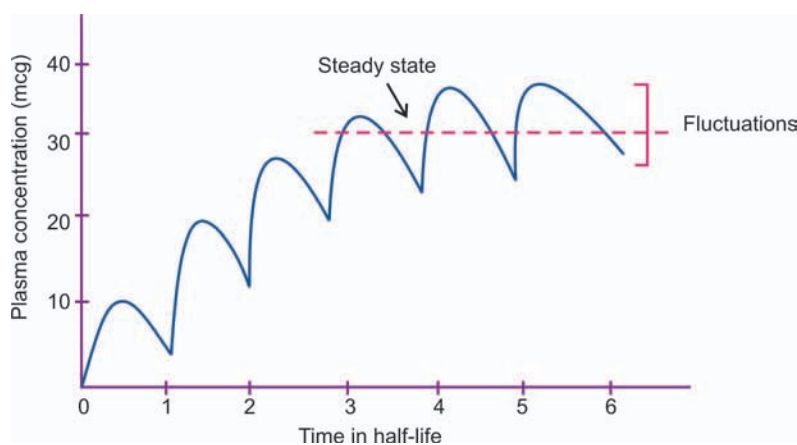


Fig. 3.8: Drug accumulation and attainment of steady state concentration on oral administration

2. to reduce the risk of toxicity, e.g. aminoglycosides.
3. when there are no reliable methods to assess benefit, e.g. antidepressants.
4. to treat poisoning.
5. when there is unexplainable therapeutic failure—to check patient compliance.

But, for drugs whose response can be easily measured, e.g. blood pressure for anti-hypertensives and for 'hit and run' drugs whose effects persist for a long time even after the drug is eliminated, monitoring of plasma drug concentration is not required.

Methods of Prolonging Drug Action (Table 3.6)

In several situations it may be desirable to use long-acting drugs. But when such drugs are not available, the duration of action of the available drugs may be prolonged.

The duration of action of drugs can be prolonged by interfering with the pharmacokinetic processes, i.e. by

1. slowing absorption.
2. using a more plasma protein bound derivative.
3. inhibiting metabolism.
4. delaying excretion.

Table 3.6: Methods of prolonging duration of action of drugs

<i>Processes</i>	<i>Methods</i>	<i>Examples</i>
Absorption		
<i>Oral</i>	Sustained release preparation, coating with resins, etc.	Iron, deriphylline
<i>Parenteral</i>	1. Reducing solubility — Oily suspension 2. Altering particle size—given as large crystals that are slowly absorbed 3. Pellet implantation — Sialistic capsules 4. Reduction in vascularity of the absorbing surface 5. Combining with protein 6. Chemical alteration — Esterification	Procaine + Penicillin Depot progestins Insulin zinc suspension DOCA Testosterone Adrenaline + lignocaine (vasoconstrictor) Protamine + zinc + insulin
<i>Dermal</i>	Transdermal adhesive patches, Ointments Ocuseris (Transmucosal) —used in eye	Oestrogen Testosterone Scopolamine Nitroglycerin
Distribution	Choosing more protein bound member of the group	Pilocarpine Sulfonamides-like sulfamethoxypyridazine
Metabolism	Inhibiting the metabolising enzyme cholinesterase By inhibiting enzyme peptidase in renal tubular cells	Physostigmine prolongs the action of acetylcholine Cilastatin—prolongs the action of imipenem
Excretion	Competition for same transport system — for renal tubular secretion	Probenecid prolongs the action of penicillin and ampicillin

4

Pharmacodynamics

Pharmacodynamics is the study of actions of the drugs on the body and their mechanisms of action, i.e. to know what drugs do and how they do it.

Drugs produce their effects by interacting with the physiological systems of the organisms. By such interaction, drugs merely modify the rate of functions of the various systems. But they cannot bring about qualitative changes, i.e. they cannot change the basic functions of any physiological system. Thus drugs act by:

1. Stimulation
2. Depression
3. Irritation
4. Replacement
5. Anti-infective or cytotoxic action
6. Modification of the immune status.

Stimulation is the increase in activity of the specialised cells, e.g. adrenaline stimulates the heart.

Depression is the decrease in activity of the specialised cells, e.g. quinidine depresses the heart; barbiturates depress the central nervous system. Some drugs may stimulate one system and depress another, e.g. morphine depresses the CNS but stimulates the vagus.

Irritation: This can occur on all types of tissues in the body and may result in inflammation, corrosion and necrosis of cells.

Replacement: Drugs may be used for replacement when there is deficiency of natural substances like hormones, metabolites

or nutrients, e.g. insulin in diabetes mellitus, iron in anaemia, vitamin C in scurvy.

Anti-infective and cytotoxic action: Drugs may act by specifically destroying infective organisms, e.g. penicillins, or by cytotoxic effect on cancer cells, e.g. anticancer drugs.

Modification of immune status: Vaccines and sera act by improving our immunity while immunosuppressants act by depressing immunity, e.g. glucocorticoids.

MECHANISMS OF DRUG ACTION

Most drugs produce their effects by binding to specific target proteins like receptors, enzymes and ion channels. Drugs may act *on* the cell membrane, *inside* or *outside* the cell to produce their effect. Drugs may act by one or more complex mechanisms of action. Some of them are yet to be understood. But the fundamental mechanisms of drug action may be:

- through receptors
- through enzymes and pumps
- through ion channels
- by physical action
- by chemical interaction
- by altering metabolic processes.

Through Receptors

Drugs may act by interacting with specific receptors in the body (see below).

Through Enzymes and Pumps

Drugs may act by inhibition of various enzymes, thus altering the enzyme-mediated

reactions, e.g. allopurinol inhibits the enzyme xanthine oxidase; acetazolamide inhibits carbonic anhydrase, enalapril inhibits angiotensin converting enzyme, aspirin inhibits cyclo-oxygenase, neostigmine inhibits acetylcholinesterase.

Membrane pumps like $H^+ K^+$ ATPase and $Na^+ K^+$ ATPase may be inhibited by drugs like omeprazole and digoxin respectively.

Through Ion Channels

Drugs may interfere with the movement of ions across specific channels, e.g. calcium channel blockers, sodium channel blockers, potassium channel openers and GABA gated chloride channel modulators.

Physical Action

The action of a drug could result from its physical properties like:

- | | |
|------------------|--|
| Adsorption | – Activated charcoal in poisoning |
| Mass of the drug | – Bulk laxatives like psyllium, bran |
| Osmotic property | – Osmotic diuretics - Mannitol |
| | – Osmotic purgatives- Magnesium sulphate |
| Radioactivity | – ^{131}I |
| Radio-opacity | – Barium sulphate contrast media. |

Chemical Interaction

Drugs may act by chemical reaction.

- | | |
|------------------|---|
| Antacids | – neutralise gastric acids |
| Oxidising agents | – like potassium permanganate is germicidal |

- | | |
|------------------|---|
| Chelating agents | – bind heavy metals making them nontoxic. |
|------------------|---|

Altering Metabolic Processes

Drugs like antimicrobials alter the metabolic pathway in the microorganisms resulting in destruction of the microorganism, e.g. sulfonamides interfere with bacterial folic acid synthesis.

RECEPTOR

The works of Langley and Ehrlich put forth the concept of a 'receptor substance.' In the late 19th century, Langley noted that curare could oppose contraction of skeletal muscles caused by nicotine but did not block contraction due to electrical stimulation. Paul Ehrlich observed that some organic chemicals had antiparasitic activity while others with slightly different structures did not have such activity. Clark put forward a theory to explain the drug action based on the drug-receptor occupation.

Last three decades have seen an explosion in our knowledge of the receptors. Various receptors have been identified, isolated and extensively studied.

Definition A receptor is a macromolecular site on the cell with which an agonist binds to bring about a change.

Affinity is the ability of a drug to bind to a receptor.

Intrinsic activity or efficacy is the ability of a drug to elicit a response after binding to the receptor.

Agonist An agonist is a substance that binds to the receptor and produces a response. It has affinity and intrinsic activity. E.g. adrenaline is an agonist at adrenergic receptors.

Antagonist An antagonist is a substance that binds to the receptor and prevents the action of the agonist on the receptor. It has affinity

but no intrinsic activity. E.g. Tubocurarine is an antagonist at nicotinic receptors.

Partial agonist binds to the receptor but has low intrinsic activity. Pentazocine is a partial agonist at μ opioid receptors.

Inverse agonist Some drugs, after binding to the receptors produce actions opposite to those produced by a pure agonist. They are known as inverse agonists, e.g. Diazepam acting on benzodiazepine receptors produces sedation, anxiolysis, muscle relaxation and controls convulsions, while inverse agonists β -carbolines bind to the same receptors to cause arousal, anxiety, increased muscle tone and convulsions.

Ligand is a molecule which binds selectively to a specific receptor.

Spare receptors Some experiments showed that high concentration of an agonist can still produce maximal response in presence of an irreversible antagonist and this was because of the presence of 'spare' or reserve receptors. Thus it is possible to stimulate the myocardium even when 90% of the cardiac β adrenergic receptors are blocked by an irreversible β blocker.

Silent receptors are receptors to which an agonist binds but does not produce a response. Presence of such silent receptors may explain the phenomenon of tolerance.

Site The receptors may be present in the cell membrane, in the cytoplasm or on the nucleus.

Nature of receptors Receptors are proteins.

Synthesis and lifespan Receptor proteins are synthesized by the cells. They have a definite lifespan after which the receptors are degraded by the cell and new receptors are synthesized.

Functions of receptors The two functions of receptors are -

- Recognition and binding of the ligand.
- Propagation of the message.

For the above functions, the receptor has two functional domains (areas):

- i. *A ligand binding domain*—the site to bind the drug molecule.
- ii. *An effector domain*—which undergoes a change to propagate the message.

Several theories have been proposed to explain drug receptor interaction. Drug-receptor interaction has been considered to be similar to 'lock and key' relationship where the drug specifically fits into the particular receptor (lock) like a key. The rate theory proposes that the magnitude of response depends on the rate of agonist-receptor association and dissociation. The rate of receptors binding is more initially but after it reaches the peak there is a decrease.

The occupation theory suggests that the magnitude of drug response depends on the proportion of the receptors occupied by the drug. Interaction of the agonist with the receptor brings about changes in the receptor which in turn conveys the signal to the effector system. The final response is brought about by the effector system through second messengers. The agonist itself is the first messenger. The entire process involves a chain of events triggered by drug receptor interaction.

Receptor Families

On stimulation of a receptor, the time required to elicit the response varies largely from a fraction of a second in some receptors to hours and days in others. This difference is because of the variation in mechanisms involved in linking the receptor and the effector systems (transduction mechanisms). Based on this, four types or super families of receptors are identified. They are best understood with the help of Figure 4.1. The receptor types are:

1. Ion channels (ionotropic receptor)
2. G-protein coupled receptors (metabotropic receptor)

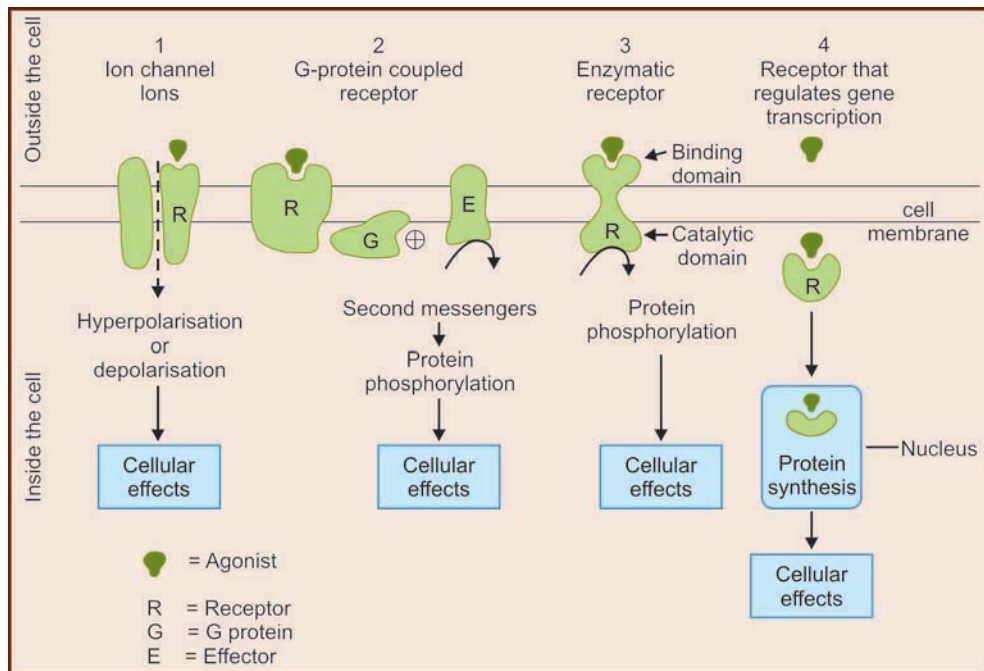


Fig. 4.1: (1) Binding of the agonist directly regulates the opening of the ion channel.
 (2) Agonist binding activates the receptor that is linked to an effector system by a G protein.
 (3) Agonist binding to extracellular domain activates enzymatic activity of its catalytic domain.
 (4) Agonist binds to the intracellular receptor, the complex moves to the nucleus and directs protein synthesis

3. Enzymatic receptors (kinase linked receptor)
4. Transcription factors (receptors that regulate gene transcription or nuclear receptors).

Receptor families and their transduction mechanisms:

1. *Ion channels* or receptor channels are proteins present on the cell surface. Binding of the agonist opens the channel allowing ions to cross the membrane. These are called ligand-gated ion channels. Depending on the ion and the channel, depolarisation/hyperpolarisation occurs, e.g. nicotinic cholinergic receptor channel permits passage of Na^+ ions resulting in depolarisation.
2. *G-protein coupled receptors* are proteins spanning the plasma membrane. The G-proteins are bound to the inner face of the

plasma membrane. The G-proteins consist of three subunits *viz.*, α , β and γ . When a ligand binds to the G-protein coupled receptor, the associated G-protein gets activated. These G-proteins acting through second messengers, bring about a chain of intracellular changes. These second messenger systems are called effector pathways. Thus G-proteins act as links or mediators between the receptors and the effector systems. They are called G-proteins because of their interaction with the guanine nucleotides, GTP and GDP. G-proteins are of different classes like G_s , G_i , G_o and G_q — G_s is stimulatory and G_i is inhibitory. The second messengers include cyclic AMP (cAMP), inositol triphosphate (IP_3), diacylglycerol (DAG), calcium and cyclic GMP (cGMP). Adrenergic receptors and muscarinic cholinergic receptors are examples of

G-protein coupled receptors.

Effector pathways through which the G-protein coupled receptors work are:

- a. Adenylylcyclase/cAMP pathway
 - b. Phospholipase C/ IP_3 -DAG pathway
 - c. Ion channel regulation
- a. *Adenylylcyclase pathway* (Fig. 4.2) Stimulation of adenylylcyclase results in the formation and accumulation of cAMP within the cell. This cAMP acts through protein kinases which phosphorylate various proteins to regulate the cell function. The response may be contraction, relaxation, lipolysis or hormone synthesis.
 - b. *Phospholipase C/ IP_3 -DAG pathway* (Fig. 4.3) Activation of phospholipase C results in the formation of second messengers IP_3 and DAG from the membrane phospholipids phosphoinositol pyrophosphate (PIP_2). IP_3 mobilises calcium from intracellular depots and this calcium mediates responses like secretion, contraction, metabolism and hyperpolarisation. DAG activates protein kinase C which regulates cell function.

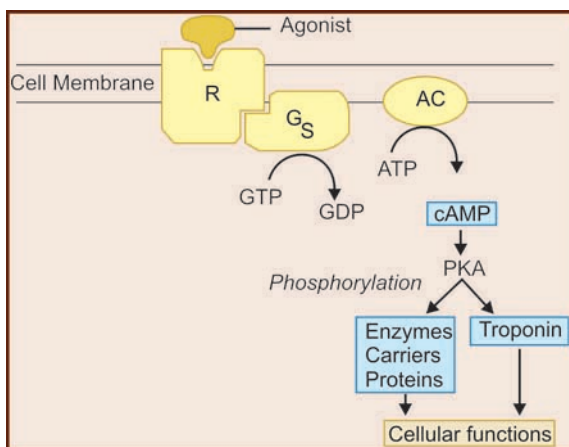


Fig. 4.2: G-protein coupled receptor - transduction through adenylylcyclase pathway with cAMP as second messenger. R = Receptor, G_s = G Protein (Stimulatory)

- c. *Ion channel regulation* The activated G-proteins can directly (without the help of second messengers) convey the signal to some ion channels causing opening or closing of the channels. The resulting responses include depolarisation/hyperpolarisation.

3. Enzymatic Receptors

These are transmembrane proteins with an extracellular domain (site) for ligand binding and intracellular domain to carry out the catalytic activity and the two domains are linked by a single peptide chain. They are protein kinases and hence are also known as **kinase linked** receptors. Binding of the agonist to the ligand binding domain results in autophosphorylation of the intracellular domain. This in turn triggers phosphorylation of various intracellular proteins resulting in the characteristic responses, Examples- receptors of insulin, leptin and growth factors including epidermal growth factors and platelet derived growth factors.

4. Receptors that Regulate Gene Transcription

These receptors are also called transcription factors or *nuclear receptors*. They are intracellular proteins which are in an inactive state. Binding of the agonist activates the receptor. The agonist-receptor complex moves to the nucleus where it interacts with DNA, regulates gene transcription and thereby directs the synthesis of specific proteins to regulate the activity of target cells. Examples are receptors for steroidal hormones, thyroid hormones, vitamin D and retinoids.

Receptor Regulation

The number of receptors (density) and their sensitivity can be altered in many situations. Denervation or prolonged deprivation of the agonist or constant action of the antagonist all result in an increase in the number and

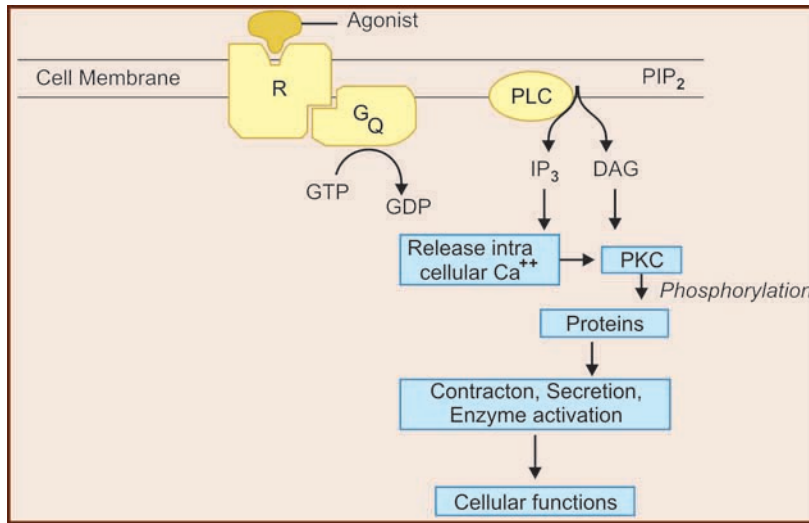


Fig 4.3: G-protein coupled receptor acting through the second messengers IP_3 and DAG

sensitivity of the receptors. This phenomenon is called '*up regulation*'.

Prolonged use of a β adrenergic antagonist like propranolol results in up regulation of β adrenergic receptors.

On the other hand, continued stimulation of the receptors causes desensitisation and a decrease in the number of receptors—known as '*down regulation*' of the receptors.

Clinical consequences and implications of receptor regulation After prolonged administration, a receptor antagonist should always be tapered. For example, if propranolol, a β adrenoceptor blocker is suddenly withdrawn after long-term use, it precipitates angina.

Constant use of β adrenergic agonists in bronchial asthma results in reduced therapeutic response due to down regulation of β_2 receptors.

Dose Response Relationship

The clinical response to the increasing dose of the drug is defined by the shape of the dose response curve (DRC). Initially the extent of response increases with increase in

dose till the maximum response is reached. The dose response curve has the shape of a rectangular hyperbola (Fig. 4.4). After the maximum effect has been obtained, further increase in doses does not increase the response. If the dose is plotted on a logarithmic scale, the curve becomes sigmoid (Fig. 4.5). The slope of DRC (Fig. 4.6) has clinical significance. A steep slope indicates that a small increase in dose produces a large increase in response, e.g. loop diuretics. Such drugs are more likely to cause toxicity and

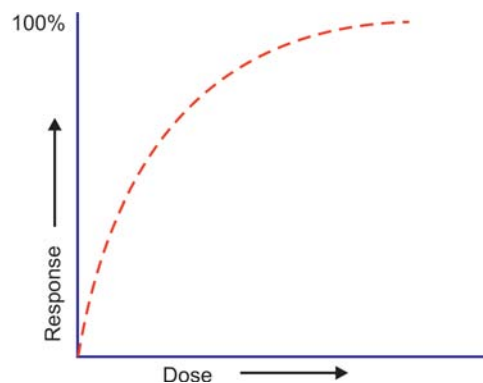


Fig. 4.4: Dose response curve

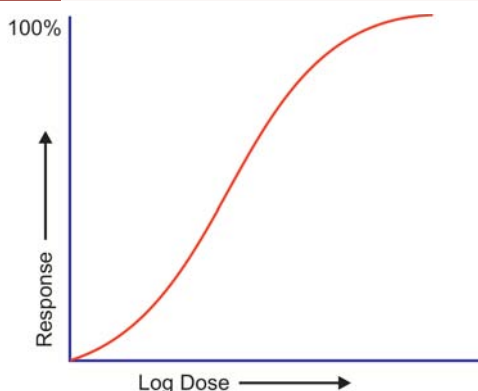


Fig. 4.5: Log dose response curve

therefore, individualisation of dose is required. A relatively flat DRC indicates that with an increase in dose, there is little increase in the response, e.g. thiazide diuretics. For such drugs standard doses can be given to most patients.

Drug Potency and Maximal Efficacy

The amount of drug required to produce a response indicates the *potency*. For example, 1 mg of bumetanide produces the same diuresis as 50 mg of frusemide. Thus bumetanide is more potent than frusemide. In Figure 4.7, drugs A and B are more potent

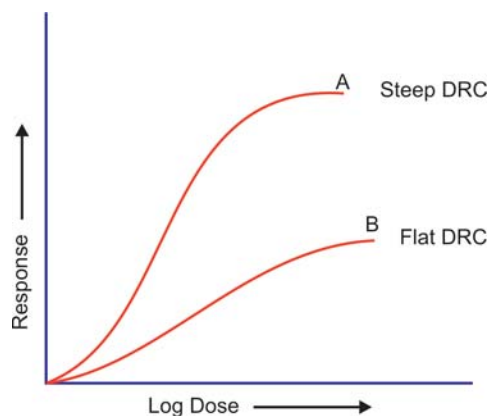


Fig.4.6: Steep and flat dose response curves

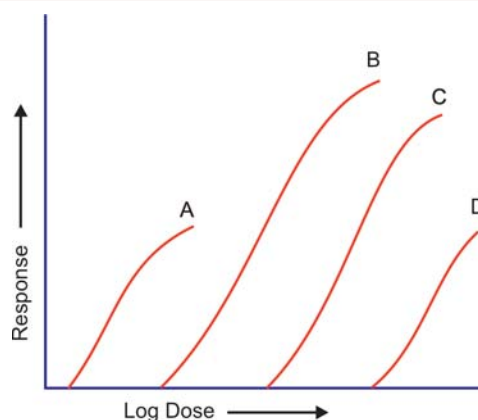


Fig. 4.7: Dose response curves of four drugs showing different potencies and maximal efficacies. Drug A is more potent but less efficacious than B and C. Drug D is less potent and less efficacious than drugs B and C

than drugs C and D, drug A being the most potent and drug D—the least potent. Hence higher doses of drugs C and D are to be administered as compared to drugs A and B. Generally potency is of little clinical significance unless very large doses of the drug needs to be given due to low potency. *Maximal efficacy* Efficacy indicates the maximum response that can be produced by a drug, e.g. frusemide produces powerful diuresis, not produced by any dose of amiloride. In Figure 4.7, drugs B and C are more efficacious than drugs A and D. Drug A is more potent but less efficacious than drugs B and C. Such differences in efficacy are of great clinical importance.

Therapeutic Index

The dose response curves for different actions of a drug could be different. Thus salbutamol may have one DRC for bronchodilation and another for tachycardia. The distance between beneficial effect DRC and unwanted effect DRC indicates the safety margin of the drug (Fig. 4.8).

Median lethal dose (LD₅₀) is the dose which is lethal to 50% of the population.

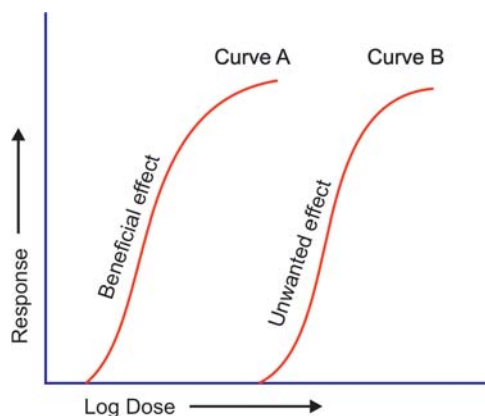


Fig. 4.8: The distance between curves A and B indicates safety margin of the drug. The greater the distance, more selective is the drug.

Median effective dose (ED_{50}) is the dose that produces a desired effect in 50% of the test population.

Therapeutic index (TI) is the ratio of the median lethal dose to the median effective dose.

$$\text{Therapeutic index} = \frac{LD_{50}}{ED_{50}}$$

Therapeutic index gives an idea about the safety of the drug.

- The higher the TI, the safer is the drug
- TI varies from species to species
- For a drug to be considered reasonably safe, its TI must be > 1
- Penicillin has a high TI while lithium and digoxin have low TI.
- TI may be different for each action of a drug. For example TI of aspirin used for headache is different from its TI for inflammation.

Therapeutic window is the plasma concentration range below which the drug is ineffective and above which toxicity appears. Hence it is desirable to have the plasma concentration of drugs within this therapeutic range. Some drugs like those with a low therapeutic index have a narrow therapeutic window. e.g. Clonidine 0.2-2.0 ng/ml. Doses of such drugs should be carefully titrated.

Drug Synergism and Antagonism

When two or more drugs are given concurrently, the effect may be additive, synergistic or antagonistic.

Additive effect The effect of two or more drugs gets added up and the total effect is equal to the sum of their individual actions. Examples are ephedrine with theophylline in bronchial asthma; nitrous oxide and ether as general anaesthetics.

Synergism When the action of one drug is enhanced or facilitated by another drug, the combination is synergistic. In Greek, *ergon* = work; *syn* = with. Here, the total effect of the combination is greater than the sum of their independent effects. It is often called 'potentiation' or 'supra-additive' effect.

Examples of synergistic combination are —

- acetylcholine + physostigmine
- levodopa + carbidopa.

Antagonism One drug opposing or inhibiting the action of another is antagonism. Based on the mechanism, antagonism can be

- Chemical antagonism
- Physiological antagonism
- Antagonism at the receptor level
 - Reversible (Competitive)
 - Irreversible
- Non-competitive antagonism.

Chemical antagonism Two substances interact chemically to result in inactivation of the effect, e.g. chelating agents inactivate heavy metals like lead and mercury to form inactive complexes; antacids like aluminium hydroxide neutralize gastric acid.

Physiological antagonism Two drugs act at different sites to produce opposing effects. For example, histamine acts on H_1 receptors to produce bronchospasm and hypotension while adrenaline reverses these effects by acting on adrenergic receptors.

Insulin and glucagon have opposite effects on the blood sugar level.

Antagonism at the receptor level The antagonist inhibits the binding of the agonist to the receptor. Such antagonism may be reversible or irreversible.

Reversible or competitive antagonism The agonist and antagonist compete for the same receptor. By increasing the concentration of the agonist, the antagonism can be overcome. It is thus *reversible antagonism*. Acetylcholine and atropine compete at muscarinic receptors. The antagonism can be overcome by increasing the concentration of acetylcholine at the receptor. d-tubocurarine and acetylcholine compete for the nicotinic receptors at the neuromuscular junction. The dose response curve shifts to the right (Fig. 4.9) in presence of competitive antagonists.

Irreversible antagonism The antagonist binds so firmly by covalent bonds to the receptor that it dissociates very slowly or not at all. Thus it blocks the action of the agonist and the blockade *cannot* be overcome by increasing the dose of the agonist and hence it is irreversible antagonism, e.g. adrenaline and phenoxybenzamine at alpha adrenergic receptors. This antagonism is also called non-equilibrium type of antagonism.

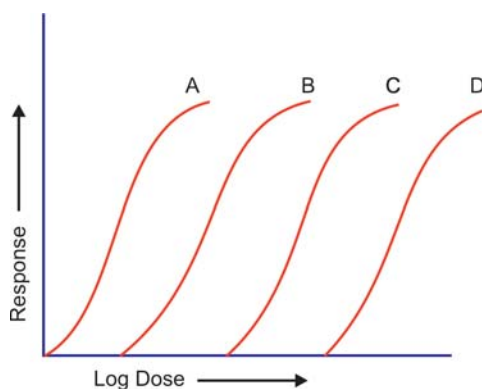


Fig. 4.9: Dose response curves of an agonist: A in the absence of competitive antagonist; B, C and D in the presence of increasing doses of a competitive antagonist

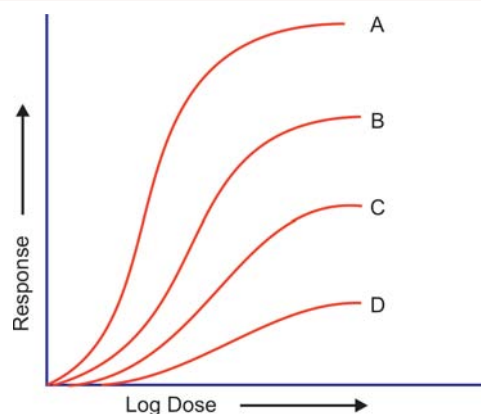


Fig. 4.10: Dose response curves of an agonist: A in the absence of antagonist. B, C, and D in the presence of increasing doses of an irreversible antagonist.

There is progressive flattening of the dose response curve (Fig. 4.10).

Noncompetitive antagonism The antagonist blocks at the level of receptor-effector linkage, i.e. at a different site, beyond the receptor and not on the receptor. There is flattening as well as some rightward shift of the dose response curve (Fig. 4.11). For example verapamil blocks the cardiac calcium channels and inhibits the entry of Ca^{++} during depolarisation. It thereby antagonises the effect of cardiac stimulants like isoprenaline and adrenaline.

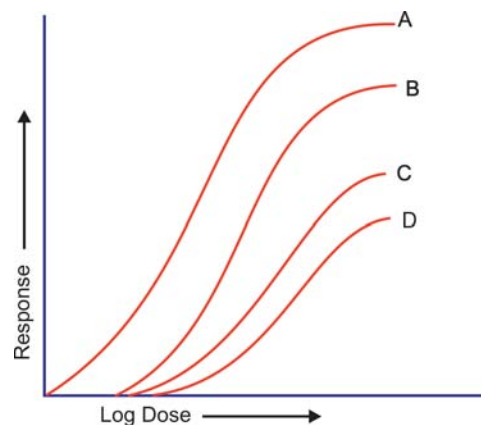


Fig. 4.11: Non-competitive antagonism—there is flattening as well as right ward shift of DRC

FACTORS THAT MODIFY THE EFFECTS OF DRUGS

The same dose of a drug can produce different degrees of response in different patients and even in the same patient under different situations. Various factors modify the response to a drug. They are:

1. *Body weight* The recommended dose is calculated for medium built persons. For the obese and underweight persons, the dose has to be calculated individually. Though body surface area is a better parameter for more accurate calculation of the dose, it is inconvenient and hence not generally used.

Formula

$$\text{Dose} = \frac{\text{Body weight (kg)}}{70} \times \text{average adult dose}$$

2. *Age* The pharmacokinetics of many drugs change with age resulting in altered response in extremes of age. In the newborn, the liver and kidneys are not fully mature to handle the drugs, e.g. chloramphenicol can produce grey baby syndrome. The blood-brain barrier is not well-formed and drugs can easily reach the brain. The gastric acidity is low, intestinal motility is slow, skin is delicate and permeable to drugs applied topically. Hence calculation of the appropriate dose based on the body weight is important to avoid toxicity. Also pharmacodynamic differences could exist, e.g. barbiturates which produce sedation in adults may produce excitation in children.

Formula for calculation of dose for children
Young's formula

$$\text{Child's dose} = \frac{\text{Age (years)}}{\text{Age} + 12} \times \text{Adult dose}$$

In the elderly, the capacity of the liver and kidney to handle the drug is reduced and they are more susceptible to adverse

effects. Hence lower doses are recommended, e.g. elderly are at a higher risk of ototoxicity and nephrotoxicity by streptomycin.

3. *Sex* The hormonal effects and smaller body size may influence drug response in women. Special care is necessary while prescribing for pregnant and lactating women and during menstruation.
4. *Species and race* Response to drugs may vary with species and race. For example, rabbits are resistant to atropine. Such variation makes it difficult to extrapolate the results of animal experiments. Blacks need higher doses of atropine to produce mydriasis.
5. *Diet and environment* Food interferes with the absorption of many drugs. For example, tetracyclines form complexes with calcium present in the food and are poorly absorbed.

Polycyclic hydrocarbons present in the cigarette smoke may induce microsomal enzymes resulting in enhanced metabolism of some drugs.

6. *Route of administration* Occasionally route of administration may modify the pharmacodynamic response, e.g. magnesium sulfate given orally is a purgative. But given IV it causes CNS depression and has anticonvulsant effects. Applied topically (poultice), it reduces local edema. Hypertonic magnesium sulfate retention enema reduces intracranial tension.
7. *Genetic factors* Variations in an individual's response to drugs could be genetically mediated. *Pharmacogenetics* is concerned with the genetically mediated variations in drug responses. The differences in response is most commonly due to variations in the amount of drug metabolising enzymes since the production of these enzymes is genetically controlled.

Examples

- a. *Acetylation of drugs* The rate of drug acetylation differs among individuals who may be fast or slow acetylators, e.g. INH, sulfonamides and hydralazine are acetylated. Slow acetylators treated with hydralazine are more likely to develop lupus erythematosus.
- b. *Atypical pseudocholinesterase* Succinylcholine is metabolised by the enzyme pseudocholinesterase. Some people inherit an atypical pseudocholinesterase which cannot quickly metabolise succinylcholine. When succinylcholine is given to such people they develop a prolonged apnoea due to persistent action of succinylcholine.
- c. *G₆PD deficiency* Primaquine, sulphones and quinolones can cause hemolysis in such people.
- d. *Malignant hyperthermia* Halothane and succinylcholine can trigger malignant hyperthermia in some genetically predisposed individuals. (page 124)
- e. *Hepatic porphyrias* Some people lack an enzyme required for haeme synthesis, and this results in accumulation of porphyrin-containing haeme precursors. Some drugs like barbiturates, griseofulvin and carbamazepine induce the enzyme required for porphyrin synthesis resulting in accumulation of porphyrins. In both the above cases neurological, gastrointestinal and behavioural abnormalities can occur due to excess porphyrins.
8. *Dose* It is fascinating that the response to a drug may be modified by the dose administered. Generally as the dose is increased, the magnitude of the response also increases proportionately till the 'maximum' is reached. Further increases in doses may with some drugs produce effects opposite to their lower-dose effect, e.g. (i) in myasthenia gravis, neostigmine enhances muscle power in therapeutic doses, but in high doses it causes muscle paralysis, (ii) physiological doses of vitamin D promotes calcification while hypervitaminosis D leads to decalcification.
9. *Diseases* Presence of certain diseases can influence drug responses, e.g.
 - *Malabsorption* Drugs are poorly absorbed.
 - *Liver diseases* Rate of drug metabolism is reduced due to dysfunction of hepatocytes. Also protein binding is reduced due to low serum albumin.
 - *Cardiac diseases* In CCF, there is edema of the gut mucosa and decreased perfusion of liver and kidneys. These may result in cumulation and toxicity of drugs like propranolol and lignocaine.
 - *Renal dysfunction* Drugs mainly excreted through kidneys are likely to accumulate and cause toxicity, e.g. Streptomycin, amphotericin B—doses of such drugs need to be reduced.
10. *Repeated dosing* can result in
 - cumulation
 - tolerance
 - tachyphylaxis.

Cumulation Drugs like digoxin which are slowly eliminated may cumulate resulting in toxicity.

Tolerance Tolerance is the requirement of higher doses of a drug to produce a given response. Tolerance may be natural or acquired.

- *Natural tolerance* The species/race shows less sensitivity to the drug, e.g. rabbits show tolerance to atropine; Black race are tolerant to mydriatics.

- *Acquired tolerance* develops on repeated administration of a drug. The patient who was initially responsive becomes tolerant, e.g. barbiturates, opioids and nitrites produce tolerance.

Tolerance may develop to some actions of the drug and not to others, e.g. morphine—tolerance develops to analgesic and euphoric effects of morphine but not to its constipating and miotic effects. Barbiturates—tolerance develops to sedative but not antiepileptic effects of barbiturates.

Mechanisms The mechanisms of development of tolerance could be:

Pharmacokinetic Changes in absorption, distribution, metabolism and excretion of drugs may result in reduced concentration of the drug at the site of action and is also known as dispositional tolerance, e.g. barbiturates induce microsomal enzymes and enhance their own metabolism.

Pharmacodynamic Changes in the target tissue, may make it less responsive to the drug. It is also called functional tolerance. It could be due to down regulation of receptors as in opioids or due to compensatory mechanisms of the body, e.g. blunting of response to some antihypertensives due to salt and water retention.

Cross tolerance is the development of tolerance to pharmacologically related drugs, i.e. to drugs belonging to a particular group. Thus chronic alcoholics also show tolerance to barbiturates and general anaesthetics.

Tachyphylaxis is the rapid development of tolerance. When some drugs are administered repeatedly at short intervals, tolerance develops rapidly and is known as tachyphylaxis or acute tolerance, e.g. ephedrine, amphetamine, tyramine and 5-hydroxytryptamine. This is thought to be due to depletion of noradrenaline stores as the above drugs act by displacing norad-

renaline from the sympathetic nerve endings. Other mechanisms involved may be slow dissociation of the drug from the receptor thereby blocking the receptor. Thus ephedrine given repeatedly in bronchial asthma may not give the desired response.

11. *Psychological factor*—The doctor-patient relationship influences the response to a drug often to a large extent by acting on the patient's psychology. The patient's confidence in the doctor may itself be sufficient to relieve a suffering, particularly the psychosomatic disorders. This can be substantiated by the fact that large number of patients respond to placebo. *Placebo* is the inert dosage form with no specific biological activity but only resembles the actual preparation in appearance (dummy medication). *Placebo* means 'I shall be pleasing' (in Latin).

Placebo medicines are used in -

1. clinical trials as a control to compare and assess whether the new compound is significantly better than the placebo.
2. to benefit or please a patient psychologically when he does not actually require an active drug as in mild psychosomatic disorders and in chronic incurable diseases.

In fact all forms of treatment including physiotherapy and surgery have some placebo effect. Substances used as placebo include lactose, some vitamins, minerals and distilled water injections.

12. *Presence of other drugs* The concurrent use of two or more drugs can influence the response of each other (see Drug Interactions Chapter No 5).

5 Adverse Drug Reactions, Drug Interactions, Drug Nomenclature and Essential Drugs Concept

ADVERSE DRUG REACTIONS

All drugs can produce unwanted effects. WHO has defined an adverse drug reaction as “any response to a drug that is noxious and unintended and that occurs at doses used in man for prophylaxis, diagnosis or therapy.”

All drugs can cause adverse effects. Some patients are more likely to exhibit adverse effects to drugs. *Pharmacovigilance* deals with the epidemiologic study of adverse drug effects.

1. Side Effects

Side effects are unwanted effects of a drug that are extension of pharmacological effects and are seen with the therapeutic dose of the drug. They are predictable, common and can occur in all people, e.g. hypoglycaemia due to insulin; hypokalaemia following frusemide.

2. Toxic Effects

Toxic effects are seen with higher doses of the drug and can be serious, e.g. morphine causes respiratory depression in overdose.

3. Intolerance

Drug intolerance is the inability of a person to tolerate a drug and is unpredictable. Patients show exaggerated response to even small doses of the drug, e.g. vestibular

dysfunction after a single dose of streptomycin may be seen in some patients. Intolerance could also be qualitative, e.g. idiosyncrasy and allergic reactions.

Idiosyncrasy is a genetically determined abnormal reaction to a drug, e.g. primaquine and sulfonamides induce haemolysis in patients with G6PD deficiency; some patients show excitement with barbiturates. In addition, some responses like chloramphenicol-induced agranulocytosis, where no definite genetic background is known, are also included under idiosyncrasy. In some cases the person may be highly sensitive even to low doses of a drug (e.g. a single dose of quinine can produce cinchonism in some) or highly insensitive even to high doses of the drug.

Allergic reactions to drugs are immunologically-mediated reactions which are not related to the therapeutic effects of the drug. The drug or its metabolite acts as an antigen to induce antibody formation. Subsequent exposure to the drug may result in allergic reactions. The manifestations of allergy are seen mainly on the target organs *viz.* skin, respiratory tract, gastrointestinal tract, blood and blood vessels.

Types of Allergic Reactions and their Mechanisms

Drugs can induce both types of allergic reactions *viz* humoral and cell-mediated immunity. Mechanisms involved in type I, II and III are humoral while type IV is by cell-mediated immunity.

Type I (Anaphylactic) reaction The drug induces the synthesis of IgE antibodies which are fixed to the mast cells. On subsequent exposure, the antigen-antibody complexes cause degranulation of mast cells releasing the mediators of inflammation like histamine, leukotrienes, prostaglandins and platelet-activating factor. These are responsible for the characteristic signs and symptoms of anaphylaxis like bronchospasm, laryngeal edema and hypotension which could be fatal. Allergy develops within minutes and is called immediate hypersensitivity reaction, e.g. penicillins. Skin tests may predict this type of reactions. Penicillins, cephalosporins, lignocaine, procaine, iron dextran and streptomycin are some drugs known to cause anaphylaxis.

Type II (Cytolytic) reactions The drug binds to a protein and together they act as antigens and induce the formation of antibodies. The antigen antibody complexes activate the complement system resulting in cytolysis causing thrombocytopenia, agranulocytosis and aplastic anaemia. Examples are carbamazepine, phenytoin, sulphonamides and phenylbutazone. Mismatched blood transfusion reactions are also cytolytic reactions.

Type III (Arthus) reactions The antigen binds to circulating antibodies and the complexes are deposited on the vessel wall where it initiates the inflammatory response resulting in vasculitis. Rashes, fever, arthralgia, lymphadenopathy, serum sickness and Stevens-

Johnson syndrome are some of the manifestations of arthus type reactions. Serum sickness is characterized by fever, arthritis, nephritis, oedema and skin rashes. Penicillins, sulfonamides, phenytoin, streptomycin and heparin can cause serum sickness. Stevens-Johnson syndrome (SJS) is characterized by severe bullous erythema multiformae particularly in the mucous membranes with fever and malaise. Toxic Epidermal Necrolysis (TEN) is the most serious form of drug allergy with cutaneous reactions that can be fatal. Aminopenicillins, sulphonamides, phenytoin, barbiturates, carbamazepine and phenylbutazone are the drugs associated with SJS and TEN.

Type IV (Delayed hypersensitivity) reactions are mediated by T-lymphocytes and macrophages. The antigen reacts with receptors on T-lymphocytes which produce lymphokines leading to a local allergic reaction, e.g. contact dermatitis in nurses and doctors handling penicillins and local anaesthetics.

4. Iatrogenic Diseases (Physician Induced)

These are drug induced diseases. Even after the drug is withdrawn, toxic effects can persist, e.g. isoniazid induced hepatitis; chloroquine induced retinopathy. Drugs like chlorpromazine, haloperidol and other phenothiazines and metoclopramide and reserpine can induce parkinsonism.

5. Drug Dependence

Drugs that influence the behaviour and mood are often misused to obtain pleasurable effects. Repeated use of such drugs result in dependence. Several words like drug abuse, addiction and dependence are used confusingly. Drug dependence is a state of compulsive use of drugs in spite of the knowledge of the risks associated with its use. It is also referred to as drug addiction. Dependence could be 'psychologic' or 'physical' dependence. Psychologic

dependence is compulsive drug-seeking behaviour to obtain its pleasurable effects, e.g. cigarette smoking.

Physical dependence is said to be present when withdrawal of the drug produces adverse symptoms. The body undergoes physiological changes to adapt itself to the continued presence of the drug in the body. Stopping the drug results in 'withdrawal syndrome.' The symptoms of withdrawal syndrome are disturbing and the person then craves for the drug, e.g. alcohol, opioids and barbiturates.

Mild degree of physical dependence is seen in people who drink too much of coffee.

6. Teratogenicity

Teratogenicity is the ability of a drug to cause foetal abnormalities when administered to a pregnant woman. *Teratos* in Greek means monster. The sedative thalidomide taken during early pregnancy for relief from

morning sickness resulted in thousands of babies being born with phocomelia (seal limbs). This thalidomide disaster (1958-61) opened the eyes of drug licensing authorities and various nations made it mandatory to conduct strict teratogenicity tests before a new drug is approved for use.

Depending on the stage of pregnancy during which the teratogen is administered, it can produce various abnormalities.

- (i) Conception to 16 days—Usually resistant to teratogenic effects. If affected, abortion occurs.
- (ii) Period of organogenesis— (17 to 55 days of gestation) - Most vulnerable period; major physical abnormalities occur.
- (iii) Foetal period—56 days onwards is the period of growth and development—hence developmental and functional abnormalities result.

Table 5.1: Examples of drugs affecting various organ systems

<i>Organ system affected</i>	<i>Examples</i>
1. Hepatotoxicity	Isoniazid, pyrazinamide, paracetamol, chlorpromazine, 6-Mercaptopurine, halothane, ethanol, phenylbutazone
2. Nephrotoxicity	Analgesics, aminoglycosides, cyclosporine, cisplatin, cephelexin, penicillamine, gold salts
3. Ototoxicity	Aminoglycosides, frusemide
4. Ocular toxicity	Chloroquine, ethambutol
5. Gastrointestinal system	Opioids, broad spectrum antibiotics
6. Cardiovascular system	Digoxin, doxorubicin
7. Respiratory system	Aspirin, bleomycin, busulfan, amiodarone, methotrexate
8. Musculoskeletal system	Corticosteroids, heparin
9. Behavioural toxicity	Corticosteroids, reserpine
10. Neurological system	INH, haloperidol, ethambutol, quinine, doxorubicin, vincristine
11. Dermatological toxicity	Doxycycline, sulfonamides, gold, d-penicillamine
12. Electrolyte disturbances	Diuretics, mineralocorticoids
13. Haematological toxicity	Chloramphenicol, sulfonamides
14. Endocrine disorders	Methyldopa, oral contraceptives

Therefore, in general, drugs should be avoided during pregnancy specially in the first trimester. The type of malformation also depends on the drug, e.g. thalidomide causes phocomelia; tetracyclines cause deformed teeth; sodium valproate causes spina bifida—See Table 5.1 for the organ systems affected.

7. Carcinogenicity and Mutagenicity

Some drugs can cause cancers and genetic abnormalities. For example anticancer drugs can themselves be carcinogenic; other examples are radioactive isotopes and some hormones.

8. Other Adverse Drug Reactions

Drugs can also damage various organ systems.

DRUG INTERACTIONS

Definition Drug interaction is the alteration in the duration or magnitude of the pharmacological effects of one drug by another drug.

When two or more drugs are given concurrently, the response may be greater or lesser than the sum of their individual effects. Such responses may be beneficial or harmful. For example a combination of drugs is used in hypertension—hydralazine + propranolol for their beneficial interaction. But unwanted drug interactions may result in severe toxicity. Such interactions can be avoided by adequate knowledge of their mechanisms and by judicious use of drugs. Some important drug interactions are mentioned in Appendix-1.

Site Drug interactions can occur:

- (i) *In vitro* in the syringe before administration—mixing of drugs in syringes can cause chemical or physical interactions—such drug combinations are incompatible in solution, e.g. penicillin and gentamicin should never be mixed in the same syringe.

- (ii) *In vivo*, i.e. in the body after administration.

Pharmacological basis of drug interactions The two major mechanisms of drug interactions include pharmacokinetic and pharmacodynamic interactions.

Pharmacokinetic mechanisms Alteration in the extent or duration of response may be produced by influencing absorption, distribution, metabolism or excretion of one drug by another.

Absorption of drugs from the gut may be affected by:

- (i) **Binding**—Tetracyclines chelate iron and antacids resulting in reduced absorption. Cholestyramine is a bile acid binding resin which also binds many drugs.
- (ii) **Altering gastric pH**—Antacids raise gastric pH and interfere with the absorption of drugs like iron and anticoagulants.
- (iii) **Altering GI motility**. Atropine and morphine slow gastric emptying and delay the absorption of drugs. Purgatives reduce the absorption of riboflavin.

Distribution Competition for plasma protein or tissue binding results in displacement interactions, e.g. warfarin is displaced by phenylbutazone from protein binding sites.

Metabolism Enzyme induction and inhibition of metabolism can both result in drug interactions (page 18), e.g. phenytoin, phenobarbitone, carbamazepine and rifampicin are enzyme inducers while chloramphenicol and cimetidine are some enzyme inhibitors.

Excretion When drugs compete for the same renal tubular transport system, they prolong each other's duration of action, e.g. penicillin and probenecid.

Pharmacodynamic mechanisms Drugs acting on the same receptors or physiological systems result in additive, synergistic or

antagonistic effects. Many clinically important drug interactions have this basis. Examples are-

- Atropine opposes the effects of physostigmine.
- Naloxone antagonises morphine.
- Antihypertensive effects of β blockers are reduced by ephedrine or other vasoconstrictors present in cold remedies.
- Many diuretics produce hypokalaemia which potentiate digitalis toxicity.
- Organic nitrates (used in angina) act by increasing cGMP activity. Sildenafil inhibits phosphodiesterase which inactivates cGMP and thereby potentiates the effects of nitrates. Hence the combination can cause severe hypotension and even deaths have been reported.
- Aspirin inhibits platelet aggregation and enhances the risk of bleeding due to oral anticoagulants like warfarin.
- Many antihistamines produce sedation which may be enhanced by alcohol intake.

Drug Nomenclature

A drug can have three names.

1. Chemical name
2. Nonproprietary (generic) name
3. Proprietary (brand) name.

The *chemical name* gives the chemical description of the drug, e.g. 3, (10, 11-dihydro-5H-dibenz (b,f) -azepin-5-yl) propyldimethylamine. This is lengthy, complex and unsuitable for prescribing.

The *nonproprietary name* is given by an official agency like WHO and is internationally accepted, i.e. the drug has the same generic name all over the world. It gives a clue to the class of the drug, because they sound similar as they end with the same letters, e.g. propranolol, atenolol, esmolol, metoprolol—all are β -blockers and cimetidine, ranitidine, famotidine and roxatidine are all H_2 receptor

blockers. It is convenient and the drug is sometimes cheaper when prescribed by generic name. The nonproprietary name of the above example given under chemical name is imipramine.

Proprietary name is the brand name given by the manufacturer. Hence each drug may have many brand names, e.g. Crocin, Metacin, Pacemol, Calpol are different brand names of paracetamol. The main advantage in using brand name is the consistency of the product especially bioavailability. Hence, for drugs with low therapeutic index like digoxin and antiepileptics, prescribing the same brand name is beneficial.

Essential Drugs Concept

WHO has compiled a list of drugs that are required to meet the primary health care needs of majority of the population and are called *essential drugs*. Essential drugs have been defined by WHO as those that satisfy the health care needs of majority of the population and should therefore be available at all times in adequate amounts and in the appropriate dosage forms. The original list has undergone revisions and updating from time to time to meet the changing requirements. Based on the WHO guidelines for selection of essential drugs and by referring its model list, each country puts forth its national list of essential drugs.

- Adoption of the list has resulted in greater coordination in health care development.
- The list serves as a guideline for indenting and stocking essential drugs.
- The concept has also helped in the development of national formularies.
- A short list is compiled for community health workers to aid in providing primary health care.
- The use of Essential Drug List has also emphasised the need for drug research and

development, e.g. safety and efficacy of a new drug should be established for it to be included in the essential drugs list. India's first National Essential Drugs List

consisting of about 300 drugs was formulated in 1996. The revised tenth model list brought out by WHO is given in Appendix-2 of the first edition of this book.

SOME EXAMPLES

Drugs that are almost completely absorbed on oral ingestion

- | | |
|--------------------|------------------|
| • Diazepam | • Indomethacin |
| • Digitoxin | • Lithium |
| • Phenylbutazone | • Phenobarbitone |
| • Minocycline | • Salicylic acid |
| • Doxycycline | • Valproic acid |
| • Chlordiazepoxide | |

Prodrugs

Drug		Active metabolite
• Levodopa	→	Dopamine
• Prednisone	→	Prednisolone
• Enalapril	→	Enalaprilat
• Bacampicillin	→	Ampicillin
• Cortisone	→	Hydrocortisone
• Azathioprine	→	Mercaptopurine
• Cyclophosphamide	→	Aldophosphamide
• Zidovudine	→	Zidovudine triphosphate

Drugs which need tapering (after long-term use)

- | | |
|--------------------|-------------------|
| • β blockers | • Sedatives |
| • Glucocorticoids | • Antidepressants |
| • Antiepileptics | • Antipsychotics |
| • Clonidine | |

Drugs with very short $t_{1/2}$ (2-10 min)

- | | |
|------------------------|------------------|
| • Dobutamine | • 5-Fluorouracil |
| • Sodium nitroprusside | • Adenosine |
| • Dopamine | • Alteplase |
| • Esmolol | |

Drugs with long $t_{1/2}$

Drug	$t_{1/2}$ in days
• Chloroquine	10-24
• Etanercept	3-4
• Phenylbutazone	3-4
• Mefloquine	16-24
• Gold salts	7

Drugs with low safety margin

- | | |
|-----------|----------------|
| • Digoxin | • Theophylline |
| • Lithium | • Quinidine |

Teratogenic drugs

- | | |
|--------------------|---------------------|
| • Thalidomide | • Glucocorticoids |
| • Tetracyclines | • Androgens |
| • Sodium valproate | • Estrogens |
| • Phenytoin | • Progestins |
| • Carbamazepine | • Antithyroid drugs |
| • Phenobarbitone | • Anticancer drugs |
| • Lithium | |

Section 2

Autonomic Nervous System

6

Introduction to Autonomic Pharmacology

The nervous system is divided into central and peripheral nervous systems (Fig. 6.1). The peripheral nervous system consists of autonomic and somatic nervous systems. The autonomic nervous system (ANS) is *not under voluntary control* and therefore was so named by Langley (*Autos* = self, *nomos* = governing—in Greek). The ANS innervates the heart, the smooth muscles, the glands and the viscera and controls the functions of these organs (Fig. 6.2).

The centres for autonomic reflexes are present in the hypothalamus, medulla and spinal cord. Hypothalamus coordinates the autonomic activity.

The ANS consists of 2 major divisions—the *sympathetic* and the *parasympathetic* (Fig. 6.4). Most of the viscera have both

sympathetic and parasympathetic innervation. The two divisions have opposing effects and normally their effects are in a state of equilibrium. The prime function of the sympathetic system is to help a person to adjust to stress and prepare the body for fight or flight reactions, while the parasympathetic mainly participates in tissue building reactions. Man can still survive without sympathetic system (if maintained stress-free) but not without parasympathetic.

Autonomic Innervation

The autonomic afferents are carried in visceral nerves through nonmyelinated fibres. For example, the parasympathetic afferents are carried by the 9th and 10th

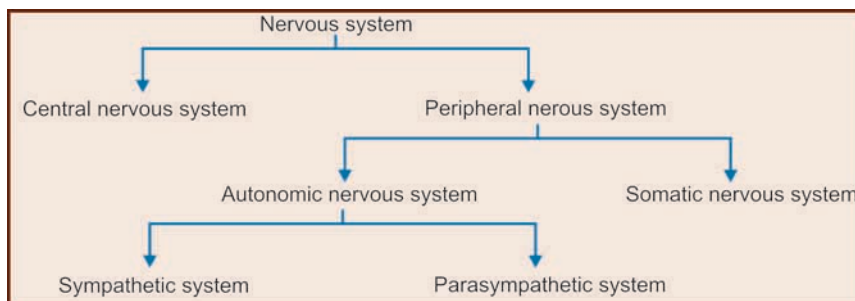


Fig. 6.1: Nervous system

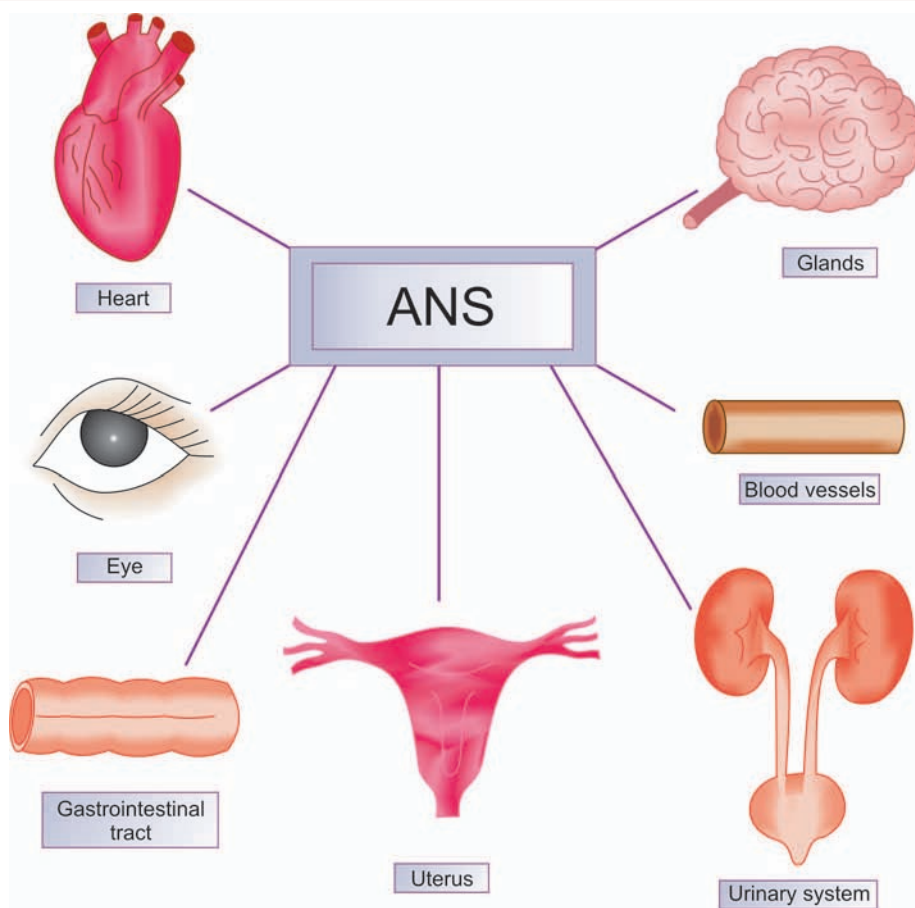


Fig. 6.2: Structures under the control of autonomic nervous system

cranial nerves. The autonomic efferent innervation (Fig. 6.3) consists of a myelinated pre-ganglionic fibre which synapses with the axon of a nonmyelinated postganglionic fibre. The postganglionic fibre in turn forms a junction with the receptors of the organs supplied by it. The junction between the pre- and postganglionic fibres is called a *ganglion* and that between the postganglionic fibres and the receptors is the *neuroeffector junction*. The travelling of an impulse along the nerve fibre is known as *conduction* while its passage across a synapse is known as *transmission*.

The autonomic efferent is divided into sympathetic and parasympathetic divisions.

The parasympathetic efferents are carried through the craniosacral outflow. The parasympathetic ganglia are located close to the innervated structures and therefore their postganglionic fibres are short. The sympathetic efferents extend from 1st thoracic to 2nd or 3rd lumbar segments (T_1 - L_3) of the spinal cord. The sympathetic ganglia are found at 3 sites—paravertebral, prevertebral and terminal. Postganglionic fibres arising from sympathetic ganglia are long and they innervate the head, neck and the viscera of the thorax and abdomen. Adrenal medulla is also considered as a sympathetic ganglion and differs from other sympathetic ganglia in that the

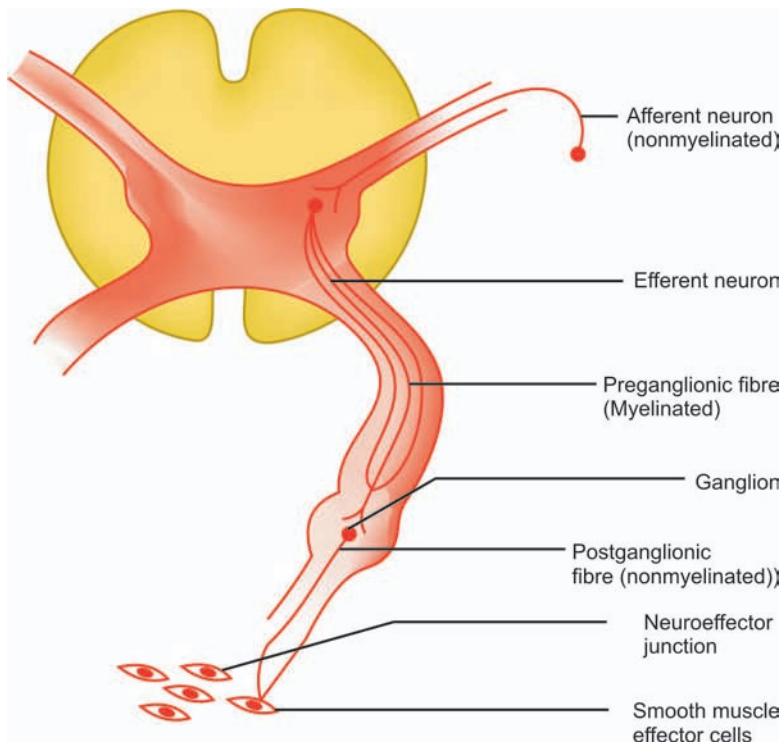


Fig. 6.3: Autonomic innervation

principal catecholamine that is released is adrenaline.

Neurotransmitters For the transmission of an impulse across a synapse, a neurohumoural transmitter substance is released into

the synaptic cleft. In the ANS, the neurotransmitters released are acetylcholine, noradrenaline, dopamine and in adrenal medulla, it is adrenaline and noradrenaline.

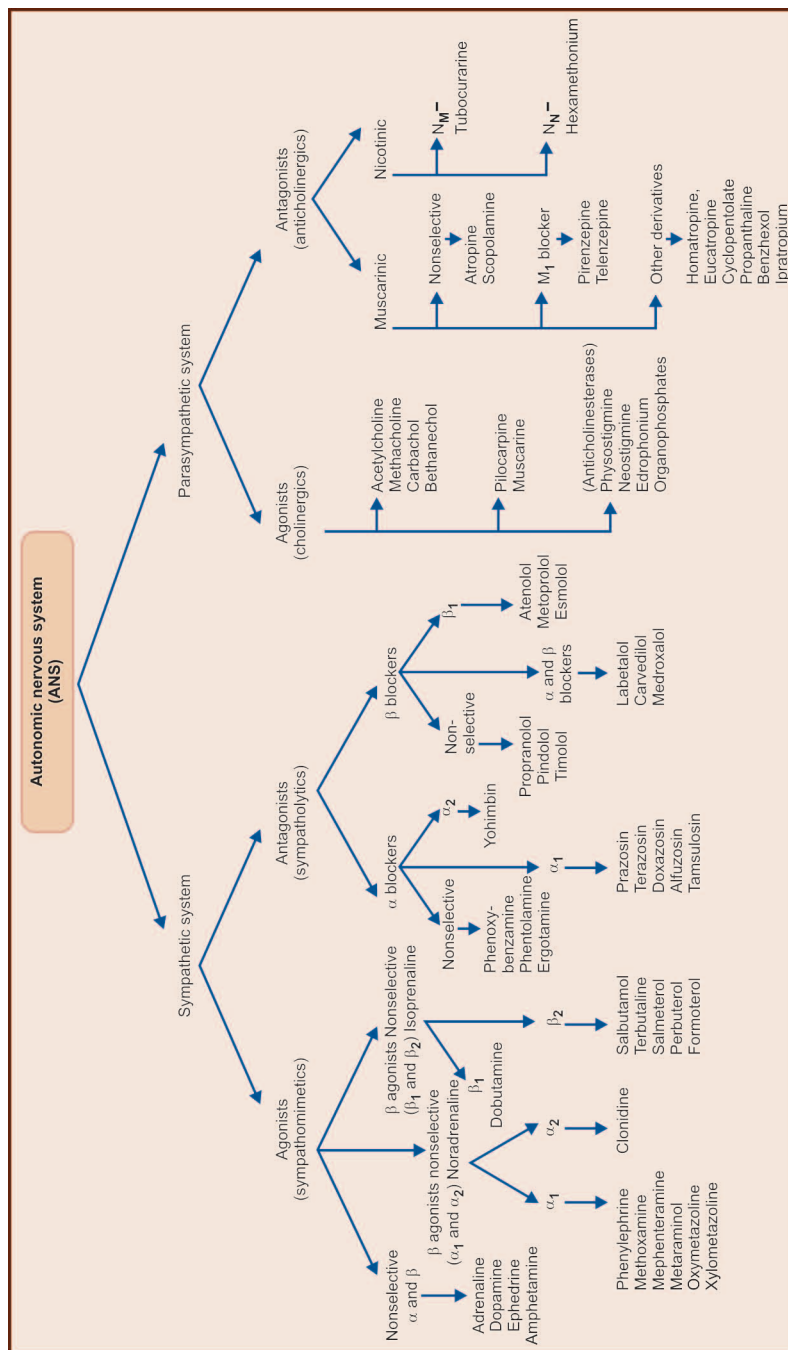


Fig. 6.4: Drugs acting on sympathetic and parasympathetic nervous system

7

Cholinergic System

Acetylcholine (ACh) an ester of choline, is the neurotransmitter of the parasympathetic system. The nerves that synthesize, store and release ACh are called '*cholinergic*.'

The sites of release of acetylcholine are (Fig. 7.1):

1. Ganglia—All the preganglionic fibres of ANS, i.e. at both the sympathetic and parasympathetic ganglia.
2. The postganglionic parasympathetic nerve endings.
3. Sweat glands—The sympathetic postganglionic nerve endings supplying the sweat glands.
4. Skeletal muscles—somatic nerve endings supplying skeletal muscles.
5. Adrenal medulla.
6. CNS—brain and spinal cord.

Synthesis of Acetylcholine Acetylcholine is synthesized from acetyl-CoA and choline,

catalysed by the enzyme choline acetyltransferase. This ACh is stored in small oval vesicles in the cholinergic nerve terminals.

Transmission of an impulse When an action potential reaches the presynaptic membrane, ACh is released into the synaptic cleft (Fig. 7.2). This ACh binds to and activates the cholinergic receptor on the postsynaptic membrane leading to the depolarisation of this membrane. Thus the impulse is transmitted across the synapse.

ACh released into the synaptic cleft is rapidly destroyed by the enzyme acetylcholinesterase (AChE). Then the post-synaptic membrane is repolarised.

Cholinesterases Acetylcholine is hydrolysed to choline and acetic acid by the enzymes cholinesterases. Two types of AChE are present:

1. True cholinesterase – at neurons, ganglia and neuromuscular junction.
2. Pseudocholinesterase (butyrylcholinesterase) – in plasma, liver and other organs.

Cholinergic receptors There are two classes of cholinergic receptors – *muscarinic* and *nicotinic*. Muscarinic receptors are present in the heart, smooth muscles, glands, eyes and CNS. Muscarinic receptors are G protein coupled receptors. Five subtypes of muscarinic receptors, M_1 - M_5 are recognised (Table 7.1).

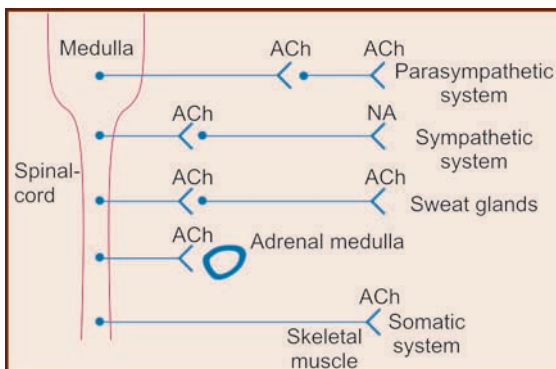


Fig. 7.1: Sites of release of neurotransmitters—acetylcholine and noradrenaline in the peripheral nervous system

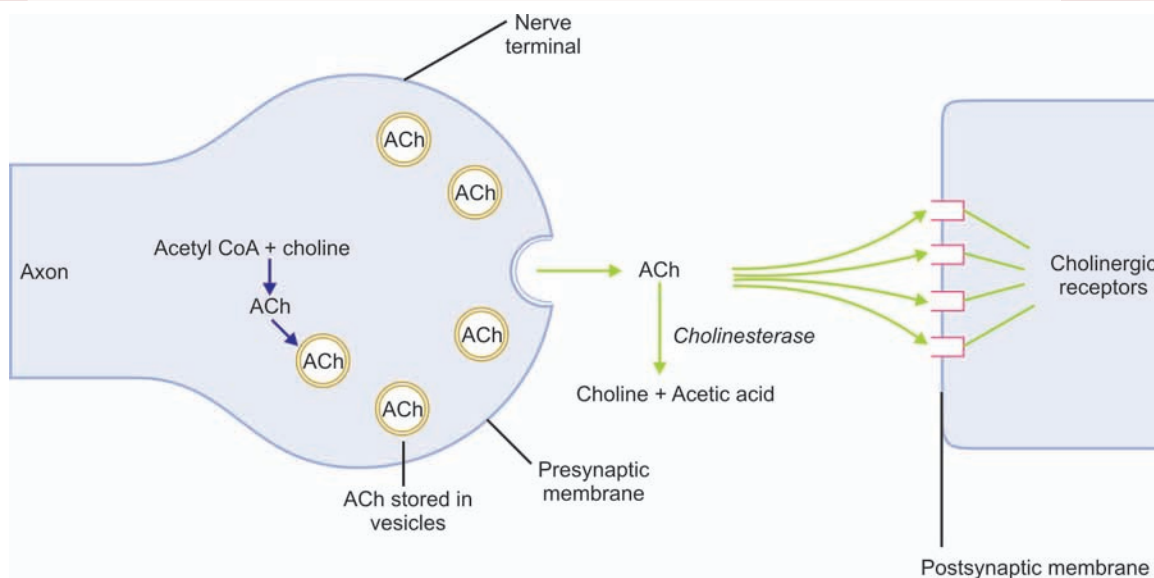


Fig. 7.2: Cholinergic transmission—schematic representation

Nicotinic receptors are present in the neuromuscular junction, autonomic ganglia and adrenal medulla. Nicotinic receptors are ion channels made of five subunits ($2\alpha+1\beta+1\gamma+1\delta$) (Fig. 7.3). Binding of acetylcholine to α subunits opens the channel allowing the entry of Na^+ into the cell. Two subtypes of nicotinic receptors are identified (Table 7.1)- N_M receptors are present at the skeletal

muscle end plate and N_N receptors at the autonomic ganglia and adrenal medulla.

CHOLINERGIC DRUGS

Cholinergic drugs are chemicals that act at the same site as acetylcholine and thereby mimic its actions. They are therefore called parasympathomimetics or cholinomimetics.

Table 7.1: Subtypes and location of cholinergic receptors

Subtypes		Location
Muscarinic	M_1	Autonomic ganglia, gastric glands, CNS
	M_2	Heart, nerves, smooth muscles
	M_3	Glands, smooth muscles
	M_4	CNS
	M_5	CNS
Nicotinic	N_M	Neuromuscular junction
	N_N	Autonomic ganglia Adrenal medulla, CNS

Cholinergic drugs may be classified as:

1. *Esters of choline*

Acetylcholine

Methacholine

Carbachol

Bethanechol

2. *Cholinomimetic alkaloids*

Pilocarpine

Muscarine

3. *Anticholinesterases*

Reversible - Neostigmine

Physostigmine

Pyridostigmine

Amibenonium

Edrophonium.

Irreversible Organophosphorus compounds.

ACTIONS OF ACETYLCHOLINE

Acetylcholine is taken as the prototype of parasymphathomimetic drugs.

Muscarinic Actions

Muscarinic actions resemble the actions of the alkaloid muscarine found in some mush-

rooms. These actions result from the stimulation of the muscarinic receptors by acetylcholine.

1. *Heart* The action of ACh is similar to that of vagal stimulation. It depresses the SA node and thereby reduces the heart rate and force of contraction. In larger doses, AV conduction is depressed.

2. *Blood vessels* ACh relaxes the vascular smooth muscles and dilates the blood vessels of the skin and mucous membrane. The BP falls due to a fall in total peripheral resistance.

3. *Smooth muscle* ACh increases the tone of all other (non-vascular) smooth muscles. *Gastrointestinal tract*—tone and peristalsis is enhanced, sphincters are relaxed, resulting in rapid forward propulsion of intestinal contents.

Urinary bladder—detrusor contracts and trigonal sphincter relaxes—promotes voiding of urine.

Bronchial smooth muscle—contracts resulting in bronchospasm.

4. *Secretory glands* Acetylcholine enhances the secretions of all glands; salivary, lacrimal, nasopharyngeal, tracheobronchial, gastric and intestinal secretions are increased. Sweating is also increased. Enhanced bronchial secretions and bronchospasm result in severe dyspnoea.

5. *Eye* Acetylcholine brings about constriction of pupil (miosis) by contracting the circular muscles of the iris (Fig. 7.4). Stimulation of muscarinic receptors present in the sphincter pupillae results in miosis. Drainage of aqueous humor is facilitated and intraocular pressure falls. Ciliary muscle contracts resulting in spasm of accommodation.

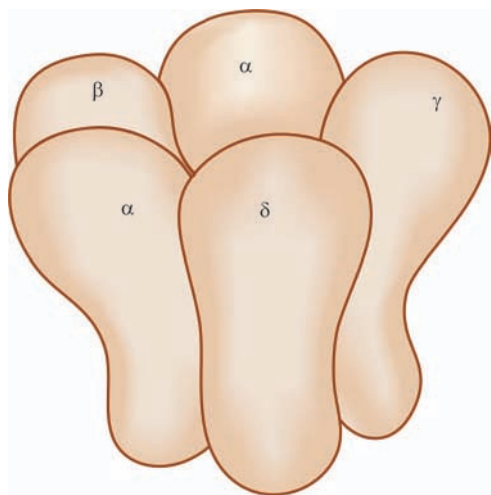


Fig. 7.3: Nicotinic receptor: Nicotinic receptor contains 5 subunits— $2\alpha + \beta + \gamma + \delta$. Acetylcholine binds to the sites on α subunits resulting in opening of the channel

Nicotinic Actions

These effects resemble the actions of the alkaloid nicotine and are brought about by stimulation of the nicotinic receptors by acetylcholine.

1. *NMJ* Acetylcholine brings about contraction of skeletal muscles by stimulating N_M receptors present in the neuromuscular junction. Large doses cause persistent depolarisation of skeletal muscles resulting in paralysis.
2. *Autonomic ganglia* Acetylcholine stimulates the sympathetic and parasympathetic ganglia and the adrenal medulla.
3. *CNS* Acetylcholine is a neurotransmitter at several sites in the CNS.

The important actions of acetylcholine are summarised in Table 7.2.

Uses Acetylcholine is destroyed in the gut when given orally. On intravenous administration, it is rapidly metabolised by pseudocholinesterases in the plasma and by true cholinesterase at the site of action. Therefore it is not used therapeutically except occasionally as 1% eyedrops to produce miosis during some eye surgeries.

Esters of choline are effective orally; carbachol and bethanechol are resistant to both cholinesterases and have a longer duration of action. Their muscarinic actions are prominent with a sustained effect on g.i. smooth muscles and urinary bladder. Methacholine is rarely used. Carbachol is used in glaucoma. Bethanechol may be used in hypotonia of bladder and g.i. smooth muscles and in some cases of postoperative paralytic ileus and urinary retention; It may also be used in xerostomia as an alternative to pilocarpine.

Table 7.2: Actions of acetylcholine

CVS	— ↓HR ↓BP
Non-vascular	— contraction, ↑gut peristalsis, promotes urine voiding
Smooth muscle	— bronchospasm
Glands	— ↑secretion
Eye	— miosis, spasm of accommodation, ↓IOP
NMJ	— muscle contraction
Ganglia	— stimulation

Adverse effects include diarrhoea, flushing, salivation, sweating, bradycardia, hypotension, syncope and bronchospasm.

CHOLINOMIMETIC ALKALOIDS

Pilocarpine is an alkaloid obtained from the leaves of *Pilocarpus microphyllus*. Like ACh it stimulates cholinergic receptors, but its muscarinic actions are prominent.

Its actions on the eye are important—when applied to the eye it causes miosis, spasm of accommodation and a fall in intraocular tension. It also increases sweat (diaphoretic) and salivary secretions (sialogogue).

Adverse effects When used as eyedrops, burning sensation and painful spasm of accommodation, browache and corneal edema can occur. Long term use can cause retinal detachment.

Uses

1. Pilocarpine is used in glaucoma (see below). Pilocarpine ocusert is available and can deliver pilocarpine constantly for 7 days.
2. Pilocarpine is also used alternately with mydriatics like homatropine to break the adhesions between the iris and the lens.
3. It is used to counter dryness of mouth that is seen following radiation of head and neck.

Glaucoma is an eye disease characterised by increased intraocular pressure. Aqueous humor is secreted by the ciliary body and it drains through the canal of Schlemm. Rise in intraocular pressure (above 30 mm of Hg) can damage the optic nerve. If untreated, irreversible damage can occur - optic nerve degenerates leading to permanent blindness. Glaucoma is one of the common causes of blindness. Hypertension, myopia and family history of glaucoma are risk factors. Glaucoma is of two types :

1. Acute congestive/narrow angle/closed angle glaucoma—in this, iris blocks the drainage of aqueous humor at the canal of Schlemm leading to increased intraocular pressure (Fig. 7.4). It needs immediate treatment.

2. Chronic simple/wide angle/open angle glaucoma—onset is slow; needs long term treatment. Surgery is the preferred option.

Two categories of drugs may be used in the treatment of glaucoma. They are -

1. Drugs that decrease the formation of aqueous humor—

Timolol	betaxolol	levobunolol
carteolol	apraclonidine	brimonidine
dipivefrine	adrenaline	acetazolamide
dorzolamide		

2. Drugs that increase the drainage of aqueous humor—

Carbachol, pilocarpine, physostigmine, echothiophate, latanoprost

Drugs used in glaucoma are summarised in Table 7.3.

- β blockers are the first line drugs. They reduce aqueous humor formation by blocking the β receptors in the ciliary body. They do not cause headache or

browache because they do not cause miosis. Even when used as eye drops, β blockers may be absorbed systemically. Hence β_1 selective agents are preferred particularly in asthmatics - even these should be used carefully.

- Epinephrine, dipivefrine and apraclonidine may act on the ciliary body to reduce aqueous humor formation. Apraclonidine is an analog of clonidine which has higher topical than systemic activity.
- Production of aqueous humor requires active transport of bicarbonate ions. Inhibition of carbonic anhydrase by acetazolamide decreases aqueous humor formation by enhancing bicarbonate loss. Acetazolamide and methazolamide are given orally but are poorly tolerated. Topical agents like dorzolamide eyedrops are now available. These can also be combined with β blockers and miotics.
- Miotics improve drainage of aqueous humor by constricting the pupil and opening the iridocorneal angle.
- Latanoprost is a prostaglandin analog (a prodrug of $\text{PGF}_{2\alpha}$). It increases the

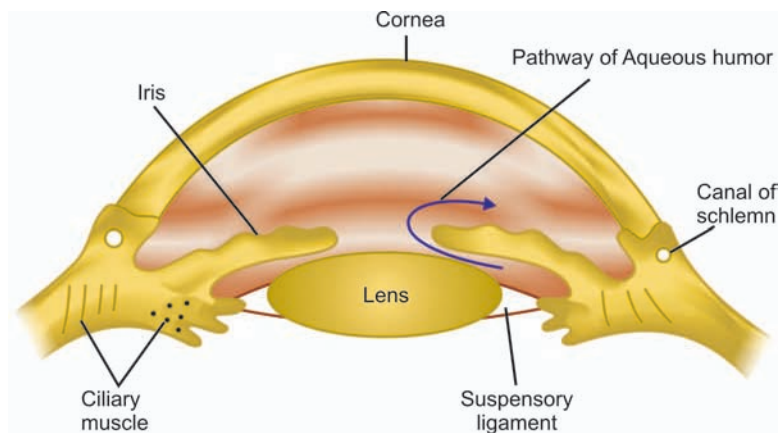


Fig. 7.4: Schematic diagram showing pathway for the drainage of aqueous humor

outflow of aqueous humor probably by relaxing the ciliary muscle. It can be used as an adjuvant to other drugs.

Acetylcholine



Choline + Acetic acid

ANTICHOLINESTERASES

Anticholinesterases (antiChEs) or cholinesterase inhibitors are drugs which inhibit the enzyme cholinesterase. As their structure resembles that of ACh, they bind to acetylcholinesterases and inactivate them.

Thus ACh is not hydrolysed and it accumulates. The actions of all these drugs are due to this accumulated ACh. Hence the actions are similar to cholinergic agonists. The structure of AChE contains an anionic

Table 7.3: Drugs used in glaucoma

<i>Drugs</i>	<i>Adverse effects</i>	<i>Comments</i>
<i>β blockers</i>		
Timolol, betaxolol carteolol, levobunolol	Conjunctival irritation, redness and discomfort	• first line drugs • No miosis-hence no head-ache or browache
<i>Cholinergics</i>		
• Pilocarpine, carbachol	Corneal edema, spasm of accommodation, browache, myopia	Used with β blockers
• Physostigmine, echothiophate	Browache, cataract, retinal detachment	
<i>Adrenergic agonists</i>		
Dipivefrine, adrenaline	Conjunctival redness, photosensitivity allergic reactions	2nd line drugs—may be combined with β blockers
<i>α₂ adrenergic agonists</i>		
Apraclonidine brimonidine	Conjunctival redness, photosensitivity	Higher topical activity than clonidine
<i>Carbonic anhydrase inhibitors</i>		
Acetazolamide, methazolamide, dorzolamide	Hypokalaemia, anorexia, drowsiness	2nd line drugs—given orally; slow release acetazolamide is better tolerated; topical dorzolamide is now available - has fewer side effects

site and an esteratic site (Fig. 7.5). Reversible anticholinesterases except edrophonium bind to both anionic and esteratic sites. Edrophonium binds only to anionic site and the binding is quickly reversible—hence it is very short acting. Organophosphates (OP)

bind only to the esteratic site but the enzyme is phosphorylated (by covalent bonds) and the binding is stable. With some OPs the binding takes many days to be reversed while with others it is not fully reversible at all.

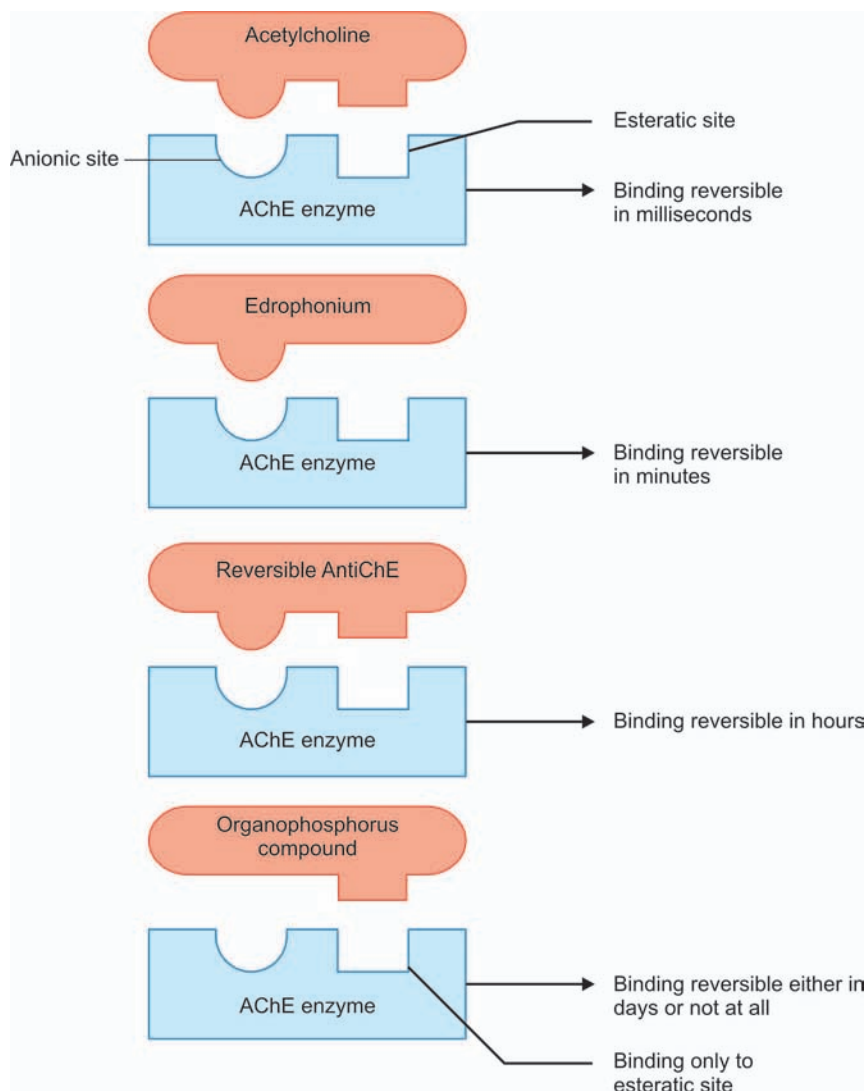


Fig. 7.5: Acetylcholine and reversible anticholinesterases bind to both anionic and esteratic sites of the acetylcholinesterase (AChE) enzyme. Edrophonium binds only the anionic site and is short acting as the binding is rapidly reversible. OP compounds bind only esteratic site but exception is echothiophate which binds both anionic and esteratic sites

Anticholinesterases are either esters of carbamic acid (carbamates) or phosphorus compounds. They may be:

1. Reversible

Physostigmine
Neostigmine
Pyridostigmine
Rivastigmine
Donepezil
Edrophonium

2. Irreversible

Organophosphates —
Echothiophate
Malathion
Sumithion
Toxic nerve gases - Sarin, Tabun
Carbamates —
Carbaryl (SEVIN)
Propoxure (BAYGON)
Aldicarb (TEMIK)

Physostigmine is an alkaloid obtained from the plant *Physostigma venenosum* (Table 7.4). It is a tertiary ammonium compound—hence has better penetration into tissues and also crosses the BBB. It is available as IV injection, as 0.1-1% eye drops and in combination with pilocarpine nitrate 2%. It is used in glaucoma and in atropine poisoning. Its use as eyedrops can cause browache and on long-term use, retinal detachment and cataract.

Neostigmine is a synthetic quaternary ammonium compound—poorly absorbed from the gut; it does not cross the BBB. It is used in myasthenia gravis, (see below) post-operative paralytic ileus and atony of the urinary bladder.

Edrophonium is rapid and short-acting. It is used in myasthenia gravis, and intravenously in snake bite and in curare poisoning.

Uses of Reversible Anticholinesterases

1. As a *miotic* Physostigmine causes miosis, spasm of accommodation and a ↓ IOP. It is used in:
 - a. Glaucoma—can be used with pilocarpine for better effect
 - b. Alternately with a mydriatic to break adhesions between the iris and the lens.
2. *Myasthenia gravis* is a chronic autoimmune disease characterised by progressive weakness with rapid and easy fatiguability of skeletal muscles. Antibodies to nicotinic receptors are formed, resulting in a decrease in the number of these receptors at NMJ. Neostigmine (15 mg tab 6 hrly) or pyridostigmine or a combination of these may be given. Edrophonium is used IV for the diagnosis. In addition to its antiChE activity, neostigmine directly

Table 7.4 : Compare and contrast physostigmine and neostigmine

Features	Physostigmine	Neostigmine
Source	Natural (<i>Physostigma venenosum</i>)	Synthetic
Chemistry	Tertiary ammonium compound	Quaternary ammonium compound
Absorption	Absorbed orally	Not absorbed
Tissue penetration	Good	Poor
BBB	Cross BBB - has CNS effect	Does not cross BBB - No CNS effects
Primary use	In glaucoma	In Myasthenia gravis
Use in poisoning	Used in atropine poisoning	Used in curare poisoning
Similarities mode of action	Cholinesterase inhibitor	Cholinesterase inhibitor

stimulates the nicotinic receptors and increases the amount of ACh released during each nerve impulse. AntiChEs enhance ACh levels at NMJ by preventing its destruction. They thus increase the force of contraction and improve muscle power by more frequent activation of the existing nicotinic receptors. In advanced disease antiChEs are not effective because the available nicotinic receptors are very few.

Factors like infection, surgery and stress can result in severe muscle weakness called-*myasthenic crisis*. But severe weakness may also result from an excess dose of an anticholinesterase drug (flaccid paralysis due to more of acetylcholine) called-*cholinergic crisis*. These two crises can be differentiated by administering edrophonium 2 mg intravenously. The patient immediately improves if it is myasthenic crisis but the weakness worsens if it is cholinergic crisis. Treatment of cholinergic crisis is with atropine while myasthenic crisis requires a higher dose of or an alternative anticholinergic drug.

Other drugs used in myasthenia gravis are

- *Glucocorticoids*—inhibit the production of antibodies to the nicotinic receptors. These are used when anticholinesterases alone are not adequate.
- *Immunosuppressants*—Azathioprine and cyclosporine can be used as alternatives to prednisolone in advanced myasthenia gravis. They inhibit the production of antinicotinic receptor antibodies.

3. *Poisoning due to anticholinergic drugs* Physostigmine is used in atropine poisoning and in toxicity due to other drugs with anticholinergic activity like phenothiazines, tricyclic antidepressants and antihistamines. Because physostigmine crosses the BBB, it reverses all the symptoms of atropine poisoning including CNS effects.

4. *Curare poisoning* Skeletal muscle paralysis caused by curare can be antagonised by AntiChEs. Though edrophonium has fast action, it is less effective than neostigmine.
5. *Postoperative paralytic ileus and urinary retention* Neostigmine may be useful.
6. *Cobra bite* Cobra venom, a neurotoxin causes skeletal muscle paralysis. Specific treatment is antivenom. Intravenous edrophonium prevents respiratory paralysis.
7. *Alzheimer's disease* - To overcome the deficient cholinergic neurotransmission, rivastigmine and donepezil are tried in Alzheimer's disease. Tacrine is another reversible anticholinesterase tried in this disease but tacrine is not preferred because it causes hepatotoxicity.

Irreversible Anticholinesterases

Organophosphorus (OP) compounds are powerful inhibitors of AChE enzyme; binding with the enzyme is stable—by covalent bonds. They bind only the esteratic site and the enzyme is phosphorylated. Effects are similar to that of cholinergic stimulation as ACh accumulates in the tissues. Organophosphates are highly lipid soluble and hence are absorbed from all routes including intact skin. This makes OP poisoning possible even while insecticides are used for spraying.

Uses

Glaucoma—echothiophate eyedrops are sometimes used in glaucoma.

Organophosphorus Poisoning

Acute Toxicity

As organophosphates are used as agricultural and domestic insecticides,

poisoning by them is quite common. Poisoning may be occupational—as while spraying insecticides, accidental or suicidal. Symptoms result from muscarinic, nicotinic and central effects; vomiting, abdominal cramps, diarrhoea, miosis, sweating, increased salivary, tracheobronchial and gastric secretions and bronchospasm; hypotension, muscular twitchings, weakness, convulsions and coma. Death is due to respiratory paralysis.

Treatment

1. If poisoning is through skin—remove clothing and wash the skin with soap and water; if consumed by oral route—gastric lavage is given.
2. Maintain BP and patent airway.
3. Drug of choice is *atropine* IV 2 mg every 10 minutes till pupil dilates. Maximum dose can be anything from 50 to 100 mg or more depending on the severity of the poisoning. Treatment should be carefully monitored because of the risk of reappearance of symptoms due to delayed absorption of the OP compounds.
4. Cholinesterase reactivators—*pralidoxime*, *obidoxime*, *diacetylmonoxime*. These oxime compounds combine with cholinesterase organophosphate complex, release the binding and set free AChE enzyme. Thus they reactivate the cholinesterase enzyme. They should be given within minutes after poisoning preferably

immediately, because the complex undergoes 'ageing' and the enzyme cannot be released. The complex becomes more stable by loss of a chemical group and this is responsible for 'ageing'. Cholinesterase reactivators are not useful in poisoning due to carbamate compounds because these compounds do not have a free site for the binding of oximes. Moreover, pralidoxime itself has weak anticholinesterase activity particularly at higher doses. In severe poisoning 1-2 g of IV pralidoxime given within five minutes of poisoning gives best results. But in practice it is rather uncommon for a patient to get such quick treatment within minutes particularly in the rural setup and cholinesterase reactivators are tried upto a few hours (maximum 24 hours) after poisoning.

Chronic Organophosphate Toxicity

Some OP compounds can produce neurotoxicity (polyneuropathy) several days after exposure to the compound. This toxicity came to light when thousands of people developed paralysis in America after consuming "Jamaica ginger" which contained small amounts of an OP compound (triorthocresylphosphate). The symptoms include weakness, fatigue, ataxia, sensory disturbances, muscle twitching and in severe cases flaccid paralysis - which may last for several years.

8

Anticholinergic Drugs

Anticholinergic drugs are agents which block the effects of acetylcholine on cholinergic receptors but conventionally antimuscarinic drugs are referred to as anticholinergic drugs. They are also called cholinergic blocking or parasympatholytic drugs. Drugs that block the nicotinic receptors are ganglion blockers and neuromuscular blockers.

Anticholinergic drugs include atropine and related drugs—atropine is the prototype.

Atropine is obtained from the plant *Atropa belladonna*. Atropine and scopolamine (hyoscine) are the belladonna alkaloids. They compete with acetylcholine for muscarinic receptors and block these receptors—they are muscarinic antagonists.

Classification

1. *Natural alkaloids*
Atropine, hyoscine (scopolamine)
2. *Semisynthetic derivatives*
Homatropine, ipratropium bromide, tiotropium bromide
3. *Synthetic substitutes*
 - Mydriatics
Eucatropine, cyclopentolate, tropicamide
 - Antispasmodic-antisecretory agents
Propantheline, dicyclomine, oxyphenonium, glycopyrrrolate, telenzepine, tolterodine, propiverine
 - Antiparkinsonian agents
Benzhexol, benztropine, trihexyphenidyl.

Actions

The actions of atropine and scopolamine are similar except that atropine is a CNS stimulant while scopolamine is a CNS depressant and causes sedation.

1. *CVS*—Atropine increases heart rate. In large doses, vasodilation and hypotension occurs.
2. *Secretions*—Atropine reduces all secretions except milk. Lacrimal, salivary, nasopharyngeal, tracheobronchial and gastric secretions are decreased. Decreased salivation results in dry mouth and difficulty in swallowing—it is an antisialogogue. Sweating is also reduced.
3. *Smooth muscle*
 - *GIT* – ↓ tone and motility and relieves spasm → may result in constipation.
 - *Biliary tract* – smooth muscles are relaxed; biliary spasm is relieved.
 - *Bronchi* – atropine causes bronchodilatation.
 - *Urinary bladder* – relaxes ureter and urinary bladder and may cause urinary retention particularly in the elderly men because they may be having prostatic hypertrophy.
4. *Eye*—On local instillation, atropine produces mydriasis by blocking the muscarinic receptors in the sphincter pupillae. The ciliary muscle is paralysed resulting in cycloplegia or paralysis of accommodation. Because of mydriasis,

Compare and contrast between atropine and scopolamine

Features	Atropine	Scopolamine
1. Source	Both are Belladonna alkaloids	
2. Chemistry	Both are tertiary ammonium compounds	
3. Mechanism of action	Both block the muscarinic receptor	
4. Source	<i>Atropa belladonna</i>	<i>Hyoscyamus nigra</i>
5. BBB	Does not readily cross Higher doses are needed to reach CNS	Readily crosses - even low doses produce CNS effects
6. Principle effect on CNS	CNS stimulation	CNS depression
7. Prominent actions on CNS	Confusion, excitement, hallucinations,	Sedation, drowsiness, ataxia, amnesia
8. Use in motion Sickness	Not used	Used.
9. Duration of action	Longer	Shorter
10. Use as cardiac vagolytic	Can be used	Not used

the iris may block the drainage of aqueous humor—IOP increases and may precipitate glaucoma in some patients.

5. CNS—In higher doses atropine stimulates the CNS resulting in restlessness, disorientation, hallucinations and delirium. In contrast, scopolamine produces sedation and drowsiness.

Pharmacokinetics Atropine and hyoscine are well-absorbed, cross the BBB and are metabolised in the liver.

Adverse effects are common but not serious and include blurring of vision, dry mouth, dysphagia, dry skin, fever, constipation and urinary retention. Skin rashes may appear. High doses cause palpitation, flushing, restlessness, delirium, hallucinations,

psychosis, convulsions and coma. Poisoning is treated with IV physostigmine.

Uses of Belladonna Alkaloids

1. *As antispasmodic*
 - In diarrhoea and dysentery, atropine relieves colic and abdominal pain.
 - In renal and biliary colic—atropine is used with morphine because atropine partly overcomes spasm of the sphincter of Oddi.
 - Nocturnal enuresis in children and in paraplegia atropine reduces urinary frequency.
2. *As mydriatic and cycloplegic*
 - **Diagnostic** for testing error of refraction and fundoscopic examination of the eye.

Drugs that can cause dryness of mouth due to anticholinergic property

- Antihistamines – e.g. Diphenhydramine
- Antipsychotics – e.g. Chlorpromazine
- Tricyclic antidepressants – e.g. Imipramine
- Atropine derivatives – e.g. glycopyrrolate

- *Therapeutic* To provide rest to the iris in iritis, iridocyclitis, keratitis and after partial iridectomy.

Mydriatics are used alternately with miotics to break adhesions between the iris and the lens - both for the treatment and prevention of adhesion formation.

3. *As pre-anaesthetic medication* When administered 30 min before anaesthesia, atropine reduces salivary and respiratory secretions. This will prevent the development of laryngospasm. It also prevents bradycardia during surgery. Its bronchodilator action is of additional value. *Glycopyrrolate* an atropine substitute, is most commonly used for this purpose.
4. *In organophosphorus poisoning* Atropine is life saving in OP poisoning and is also useful in mushroom poisoning.
5. *In bronchial asthma, peptic ulcer and parkinsonism* Atropine derivatives are preferred over atropine—see below.
6. *Motion sickness* Hyoscine given 30 minutes before the journey prevents travelling sickness. Transdermal hyoscine patches are available to be applied behind the ear for a prolonged action.

7. Hyoscine can also be used during *labour* to produce sedation and amnesia.

Drug interactions When anticholinergics are given with other drugs that also have anticholinergic property like antihistaminics, phenothiazines, tricyclic antidepressants—side effects get added up.

ATROPINE SUBSTITUTES

Belladonna alkaloids produce a wide range of effects, most of which are of therapeutic value. But these can also result in various side effects since they lack selectivity. Hence several semisynthetic and synthetic derivatives have been introduced some of which have selective actions (Table 8.1).

- Mydriasis and cycloplegia produced by atropine last for 7–10 days. The derivatives have shorter action (6–24 hrs), tropicamide being the shortest acting. Some can selectively produce either prominent mydriasis or cycloplegia.
- Antispasmodics or spasmolytics are used to relieve spasms of the gastrointestinal tract, biliary tract, ureter and uterus. They are also found to be useful in irritable

Table 8.1: Atropine substitutes

Indications	Derivatives
1. <i>On the eye - mydriatics and cycloplegics</i>	Homatropine, eucatropine cyclopentolate, tropicamide
2. <i>As antispasmodics</i>	Propantheline, methantheline, dicyclomine, flavoxate hydrochloride, oxybutynin chloride, oxyphenonium, glycopyrrolate, clidinium
3. <i>Peptic Ulcer</i>	Pirenzepine, telenzepine
4. <i>Bronchial asthma</i>	Ipratropium, tiotropium
5. <i>Preanaesthetic medication</i>	Glycopyrrolate
6. <i>Urinary disorders</i>	Oxybutynin, tolterodine, propiverine, dicyclomine
7. <i>Antiparkinsonian drugs</i>	Benzhexol, benztropine, trihexyphenidyl.

bowel syndrome. Some of them in addition, reduce gastrointestinal motility.

- Pirenzepine and telenzepine are selective M_1 blockers which inhibit gastric secretion at doses that do not affect other functions. Pirenzepine also does not cross the BBB – hence has no CNS effects. They are tried in peptic ulcer.
- When used in bronchial asthma, atropine thickens the bronchial secretions and interferes with the movement of cilia, thus favouring formation of mucus plugs. Ipratropium bromide is a bronchodilator that does not affect mucociliary activity. When given as inhalation it acts only on the airways and does not produce any significant systemic effects because it is poorly absorbed.
- Glycopyrrolate is an **antisialogogue** (reduces salivary secretions). It is a quaternary amine – does not cross the BBB – therefore no effects on the CNS. It is given IM as preanaesthetic medication and in dental practice when it is necessary to reduce salivary secretions.
- Benztropine, benzhexol and trihexyphenidyl are the derivatives used in drug induced parkinsonism.
- Urinary disorders – atropine substitutes are used to reduce urinary urgency and frequency to relieve bladder spasm and improve bladder capacity in urinary disorders and following urologic surgeries. They are also tried in nocturnal enuresis in children.

9

Skeletal Muscle Relaxants

Skeletal muscle relaxants (SMR) are drugs that reduce the muscle tone either by acting peripherally at the neuromuscular junction (neuromuscular blockers) or centrally in the cerebrospinal axis or directly on the contractile mechanism. They reduce the spasticity in a variety of neurological conditions and are also useful in surgeries.

CLASSIFICATION

Skeletal muscle relaxants may be classified as follows:

1. Drugs acting peripherally at the NMJ

Competitive blockers

(Nondepolarising agents)–

d-Tubocurarine,
pancuronium,
alcuronium,
atracurium,
mivacurium,
rocuronium,
doxacurium,
pipecuronium,
vecuronium,
rapacuronium,
gallamine

*Depolarising blockers–*Succinylcholine,
decamethonium

2. Drugs acting centrally–Diazepam, baclofen,
mephenesin,
tizanidine.

3. Drugs acting directly on the muscle–
Dantrolene.

PERIPHERALLY ACTING SKELETAL MUSCLE RELAXANTS

Neuromuscular Blockers (NMB)

Competitive Blockers

Curare was used by the South American Indians as an arrow poison for hunting wild animals because curare paralysed the animals. On extensive research, the active principle from curare, **tubocurarine** was identified.

d-tubocurarine (d-Tc) is the dextro-rotatory quaternary ammonium alkaloid obtained from the plant *Chondrodendron tomentosum* and plants of the *Strychnos* species (l-tubocurarine is less potent). Several synthetic agents have been developed. All these are quaternary ammonium compounds because of which they are not well absorbed and are quickly excreted.

Mechanism of action Non-depolarising blockers bind to nicotinic receptors on the motor end plate and block the actions of acetylcholine by competitive blockade (Fig. 9.1). These compounds slowly dissociate from the receptors and transmission is gradually restored. Thus the action of d-Tc is reversible.

Tubocurarine

Pharmacological Actions

Skeletal muscle On parenteral administration, tubocurarine initially causes muscular weakness followed by flaccid paralysis. Small muscles of the eyes and fingers are

the first to be affected, followed by those of the limbs, neck and trunk. Later the intercostal muscles and finally the diaphragm are paralysed and respiration stops. Consciousness is not affected throughout. Recovery occurs in the reverse order, i.e. the diaphragm is the first to recover. The effect lasts for 30-60 minutes (Table 9.1).

Autonomic ganglia In high doses tubocurarine can block autonomic ganglia and adrenal medulla resulting in hypotension.

Histamine release Tubocurarine can cause histamine release from the mast cells leading to bronchospasm, increased tracheo-bronchial and gastric secretions and this histamine release also contributes to hypotension.

Pharmacokinetics d-Tc is a quaternary ammonium compound—hence not absorbed orally. It is given either IM or IV.

Adverse Reactions

1. Respiratory paralysis and prolonged apnoea—Patient should be given artificial ventilation. Neostigmine may be used to reverse the skeletal muscle paralysis.
2. Hypotension is due to ganglion blockade and histamine release.
3. Flushing and bronchospasm due to histamine release by tubocurarine—this is not seen with newer agents.

Treatment of toxicity - Neostigmine (Table 9.2) may be used to reverse the skeletal muscle paralysis and it is the antidote in curare poisoning. Antihistamines should be given to counter the effects of histamine.

Synthetic Competitive Blockers

Pancuronium, atracurium, vecuronium, gallamine, doxacurium, mivacurium, pipecuronium, rapacuronium, rocuronium are (Table 9.1) synthetic NMBs. They have the following advantages over tubocurarine -

- Less/no histamine release.
- Do not block autonomic ganglia hence cause less hypotension.
- Spontaneous recovery takes place with most of these drugs.
- Some are more potent than tubocurarine.
- The newer agents rapacuronium and rocuronium have a rapid onset of action. Hence they can be used as alternatives to succinylcholine for muscle relaxation before endotracheal intubation.
- Rocuronium does not cause hypotension, tachycardia and is fast acting.
- Atracurium can be safely used in patients with renal impairment because it is degraded by plasma esterases and does not depend on the kidney for elimination. Atracurium is metabolised to a derivative which causes CNS stimulation, seizures and increases the

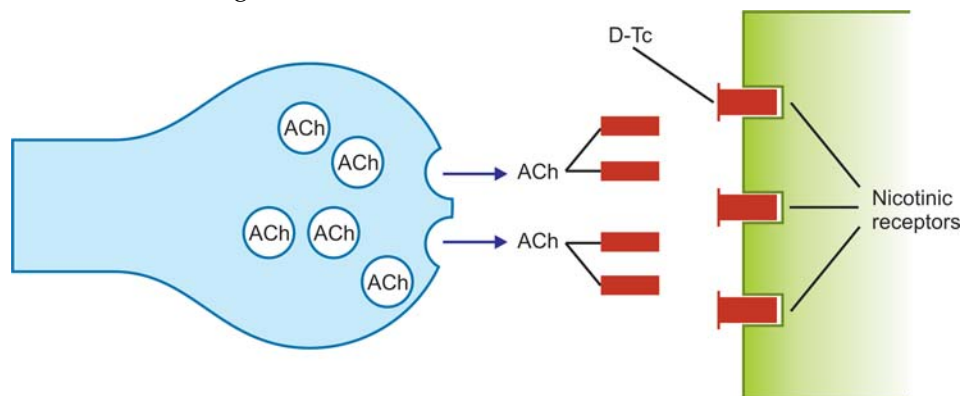


Fig. 9.1: d-Tc molecules bind to nicotinic receptors and prevent the binding of ACh on these receptors

Table 9.1: Duration of action of competitive neuromuscular blockers

Drug	Duration (min)
Tubocurarine	35-60
Gallamine	35-60
Pancuronium	35-80
Doxacurium	90-120
Atracurium	20-35
Vecuronium	20-35
Mivacurium	12-18
Pipecuronium	80-100
Rapacuronium	15-30
Rocuronium	30-60

dose of the anaesthetic needed. Cisatracurium does not form this derivative and also causes less histamine release when compared to atracurium. Therefore cisatracurium is now a preferred skeletal muscle relaxant.

- Tubocurarine, doxacurium and gallamine have a slow onset but longer duration of action (about 5 minutes). Pancuronium, vecuronium, atracurium have intermediate onset (2-4 minutes) while rapacuronium and rocuronium have fast onset of action (1-2 minutes).
- Tubocurarine causes histamine release, ganglion blockade (resulting in hypotension) and its muscle relaxant effect needs to be reversed with drugs. Hence

it is not used now. The synthetic compounds are preferred.

Depolarising Blockers

Succinylcholine (SCh, Suxamethonium) is a quaternary ammonium compound with the structure resembling two molecules of acetylcholine joined together.

Mechanism of action The neuromuscular effects of SCh are like those of ACh. SCh reacts with the nicotinic receptors (Fig. 9.2) and depolarises the skeletal muscle membrane. But, unlike ACh, it is destroyed very slowly by pseudocholinesterase. Thus continued presence of the drug causes persistent depolarisation resulting in flaccid paralysis. This is phase I block. In high doses SCh produces a dual block—initial depolarising block followed by nondepolarising block. The membrane gets slowly repolarised but cannot be depolarised again. The mechanism is not clearly known.

Pharmacological Actions

Skeletal muscle On intravenous administration onset of action is very rapid—within 1 minute. Initial transient muscular fasciculations and twitches, mostly in the chest and abdominal regions are followed by skeletal muscle paralysis. The fasciculations are maximum in 2 minutes and subside in 5 minutes. It is due to stimulation of the muscle fibres by the

Table 9.2 : Comparison and contrast d-Tubocurarine and succinylcholine

	Tubocurarine	Succinylcholine
<i>Mechanism of action</i>	Competitive blockade	Persistent depolarization
<i>Type of blockade</i>	Nondepolarising	Depolarising
<i>Phases of blockade</i>	Single	Dual block
<i>Anticholinesterases</i>	Reverse blockade	Do not reverse
<i>Initial fasciculations</i>	Nil	Present
<i>Metabolism</i>	Only partly metabolized in the liver	By pseudocholinesterase
<i>Onset of action</i>	Slow	Fast
<i>Duration of action</i>	Long (30-60 min)	Short (5-10 min)
<i>Treatment of toxicity</i>	Neostigmine	Fresh blood transfusion
<i>Action</i>	Skeletal muscle relaxant	Skeletal muscle relaxant

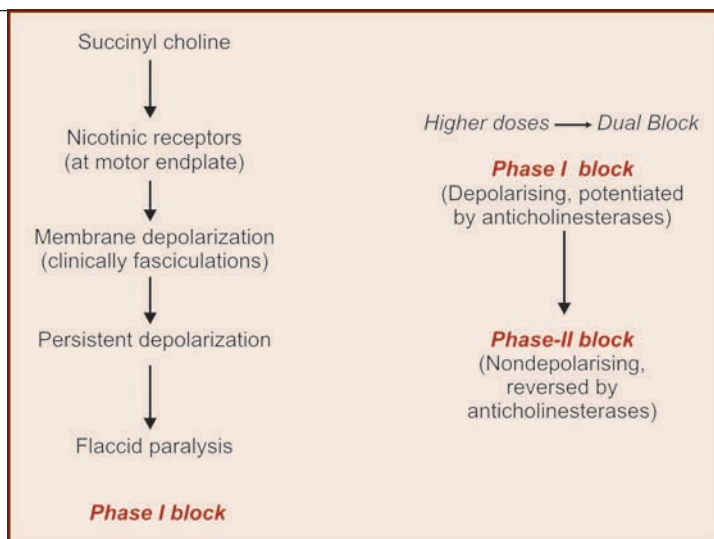


Fig. 9.2: Mechanism of action of succinylcholine

discharge of action potentials in them. SCh is a short acting muscle relaxant and the effect lasts for 5-10 minutes. Hence it has to be given continuously as an infusion for longer effect.

CVS Initially hypotension and bradycardia may result from stimulation of vagal ganglia. This is followed by hypertension and tachycardia due to stimulation of sympathetic ganglia. Higher doses can cause cardiac arrhythmias. SCh can also cause histamine release if injected rapidly.

Pharmacokinetics SCh is rapidly hydrolysed by pseudocholinesterase—hence it is short-acting—about 5 minutes. Some people (1 in 2000) have an abnormal pseudocholinesterase enzyme due to a hereditary defect. In such people, SCh does not get metabolised and even the usual dose results in prolonged apnoea and paralysis which may last for several hours. Artificial ventilation and fresh blood transfusion are needed to supply pseudocholinesterase.

Adverse Reactions

Postoperative muscle pain is a common adverse effect of SCh. It may be due to the damage

to muscle fibers that occurs during initial fasciculations.

Hyperkalaemia—Depolarising blockers can cause hyperkalaemia due to sudden release of K^+ from the intracellular sites. This can be dangerous particularly in patients with CCF. It may result in cardiac arrest in patients with burns and nerve injuries.

Cardiac arrhythmias—SCh can cause cardiac arrhythmias.

Malignant hyperthermia—is a rare genetically determined condition where there is a sudden increase in the body temperature and severe muscle spasm due to release of intracellular Ca^{++} from the sarcoplasmic reticulum. Certain drugs like halothane, isoflurane and succinylcholine can trigger the process which can be fatal. Combination of halothane and SCh is the most common triggering factor. Intravenous dantrolene is life-saving in malignant hyperthermia. Oxygen inhalation and immediate cooling of the body also help.

Drug Interactions

1. General anaesthetics augment the action of SMRs.

2. Anticholinesterases like neostigmine reverse the action of competitive blockers.
3. Aminoglycosides and calcium channel blockers potentiate the action of SMRs.

Uses of Peripherally Acting Skeletal Muscle Relaxants

Inappropriate use of peripherally acting SMRs can be fatal. Hence they should be given only by qualified anaesthetists or adequately trained doctors.

1. *Adjuvant to anaesthesia* Adequate muscle relaxation is essential during surgeries. Skeletal muscle relaxants are used as adjuvants to general anaesthesia. Short acting SMRs like succinylcholine are used during endotracheal intubation. SMRs are also useful in laryngoscopy, bronchoscopy, esophagoscopy and in orthopaedic procedures like reduction of fractures and dislocations.
2. *In electroconvulsive therapy* SMRs protect the patient from convulsions and trauma during ECT.
3. *In spastic disorders* SMRs are used to overcome the spasm of tetanus, athetosis and status epilepticus.

CENTRALLY ACTING MUSCLE RELAXANTS

These drugs act on higher centres and cause muscle relaxation without loss of consciousness. They also have sedative properties.

Mechanism of Action

Centrally acting muscle relaxants depress the spinal polysynaptic reflexes. These reflexes maintain the muscle tone. By depressing these spinal reflexes, centrally acting muscle relaxants reduce the muscle tone.

Diazepam has useful antispastic activity. It can be used in relieving muscle spasm of almost any origin including local muscle trauma (see Page 140).

Baclofen is an analog of the inhibitory neurotransmitter GABA. It is a GABA_B

agonist. It depresses the monosynaptic and polysynaptic reflexes in the spinal cord. It relieves painful spasms including flexor and extensor spasms and may also improve bladder and bowel functions in patients with spinal lesions. Normal tendon reflexes are not affected.

Baclofen is generally given orally. It should be gradually withdrawn after prolonged use because abrupt withdrawal can cause anxiety, palpitations and hallucinations.

Side effects are drowsiness, weakness and ataxia.

Mephenesin is not preferred due to its side effects. A number of related drugs like *carisoprodol*, *methocarbamol*, *chlorzoxazone* are used in acute muscle spasm caused by local trauma. All of them also cause sedation.

Tizanidine is a congener of clonidine. It is a central α_2 agonist like clonidine. It increases presynaptic inhibition of motor neurons and reduces muscle spasms. Adverse effects include drowsiness, weakness, hypotension and dry mouth. Tizanidine is used in the treatment of spasticity due to stroke, multiple sclerosis and amyotrophic lateral sclerosis.

Other centrally acting spasmolytic agents include *riluzole*, *gabapentin* and *progabide*. Riluzole has both presynaptic and postsynaptic effects. It inhibits glutamate release in the CNS. It is well tolerated with minor adverse effects like nausea and diarrhoea. It is used to reduce spasticity in amyotrophic lateral sclerosis.

Uses of Centrally Acting Muscle Relaxants

1. *Musculoskeletal disorders* like muscle strains, sprains, myalgias, cervical root syndromes, herniated disc syndromes, low backache, dislocations, arthritis, fibrositis and bursitis all cause painful muscle spasms. Muscle relaxants are used with analgesics in these conditions.
2. *Spastic neurological disorders* like cerebral palsy, multiple sclerosis, poliomyelitis,

hemiplegia and quadriplegia are treated with diazepam or baclofen.

3. *Tetanus* Diazepam is given IV.
4. *ECT* Diazepam is given along with peripherally acting SMRs.
5. *Orthopaedic* procedures like fracture reduction may be done after administering diazepam.

DIRECTLY ACTING MUSCLE RELAXANTS

Dantrolene directly affects the skeletal muscle contractile mechanism. It inhibits the muscle contraction by preventing the calcium release from the sarcoplasmic reticulum.

Adverse effects include drowsiness, dizziness, fatigue, diarrhoea, muscle weakness and rarely hepatotoxicity. Liver function tests should be done to look for hepatotoxicity.

Uses Dantrolene is used in spastic disorders like hemiplegia, paraplegia, spinal injuries, multiple sclerosis and cerebral palsy. Dantrolene is the drug of choice in malignant hyperthermia which is due to excessive release of calcium from the sarcoplasmic reticulum. Dantrolene blocks the release of Ca^{++} from the sarcoplasmic reticulum and relieves muscle spasm in malignant hyperthermia.

DRUGS USED IN THE TREATMENT OF LOCAL MUSCLE SPASM

Several agents are used for the treatment of local muscle spasms which may result from injury or strain. Cyclobenzaprine, metaxalone, carisoprodol, chlorzoxazone, meprobamate and methocarbamol are some of them. They have the following common features-

- All these drugs act by depressing spinal polysynaptic reflexes.
- Common adverse reactions include drowsiness and dizziness.
- Cyclobenzaprine has anticholinergic effects and can therefore cause dryness of mouth, drowsiness and dizziness.
- Many of them are available in combination with NSAIDs.
- NSAIDs are equally or more effective in relieving muscle spasms.

Botulinum toxin is produced by the anaerobic bacterium *Clostridium botulinum*. The toxin inhibits the release of acetylcholine at the cholinergic synapses resulting in flaccid paralysis of skeletal muscles.

Botulinum toxin is useful (local injection) in the treatment of dystonias, including sports or writer's cramps, muscle spasms, tremors, cerebral palsy and in rigidity seen in extrapyramidal disorders. It is commonly used to relieve blepharospasm (spasm of the orbicularis oculi muscle of the eyes). Botulinum toxin is also gaining popularity in cosmetic therapy to remove facial lines by local injection.

Skeletal muscle relaxants in dentistry

1. Spasm SMRs like mephenesin, diazepam and others along with analgesics are used to relieve the spasm of the masticatory muscles. Such spasm can cause pain around temporomandibular joint.
2. Dislocation—Sometimes in temporomandibular joint dislocation, just relaxing the related muscles with SMRs may be sufficient to set right the dislocation.
3. Fractures—SMRs may also be used to reduce fractures of the mandible.

10

Adrenergic System

The prime function of the adrenergic or sympathetic nervous system is to help the human being to adjust to stress and prepare the body for fight or flight reactions. When exposed to stress, the heart rate and stroke volume increase with the resultant increase in cardiac output. The blood is shifted from the skin, gut, kidney and glands to the heart, skeletal muscles, brain and lungs, as these organs need more blood during stress. Pupils and bronchi are dilated and sweating is increased. Blood glucose increases by glycogenolysis.

Neurotransmitters of the sympathetic system are noradrenaline (NA, norepinephrine) and dopamine (DA). Adrenaline (epinephrine) is the major hormone secreted by the adrenal medulla (Table 10.2).

Synthesis of catecholamines The three catecholamines—noradrenaline, adrenaline and dopamine are synthesized from the amino acid tyrosine (Fig. 10.1).

The sympathetic postganglionic nerve fibres that synthesize, store and release NA are called *adrenergic*. Noradrenaline is stored in small vesicles in the adrenergic nerve terminals (Fig. 10.2) In response to nerve impulse, NA is released into the synaptic cleft by a process called *exocytosis*. This NA binds to adrenergic receptors located on the postsynaptic membrane to produce the response. A small portion of NA is metabolised by the enzyme COMT but a large portion (nearly 80%) is taken back into the

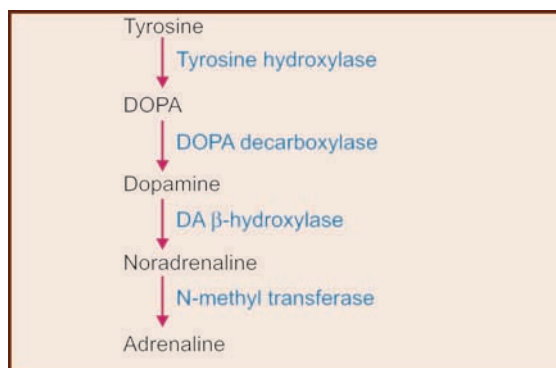


Fig. 10.1: Biosynthesis of catecholamines

nerve terminals by an active transport process termed *uptake 1*, which is responsible for termination of action of NA. Of this portion which is taken up, a fraction is metabolised by MAO and the remaining NA is then transferred to the storage vesicles. Some part of NA released into the synaptic cleft penetrates into the effector cells and is known as *uptake 2*.

Adrenergic receptors Ahlquist classified adrenergic receptors into 2 types— α and β . With the availability of newer, synthetic, selective drugs, these are further classified into subdivisions. We now know α_1 , α_2 , β_1 , β_2 and β_3 adrenergic receptors.

The stimulation of α receptors mainly produces excitatory effects (exception-GIT); β stimulation causes mainly inhibitory effects (exception- heart). The characteristics of these receptors are given in Table 10.1. α_2 receptors are located on the presynaptic

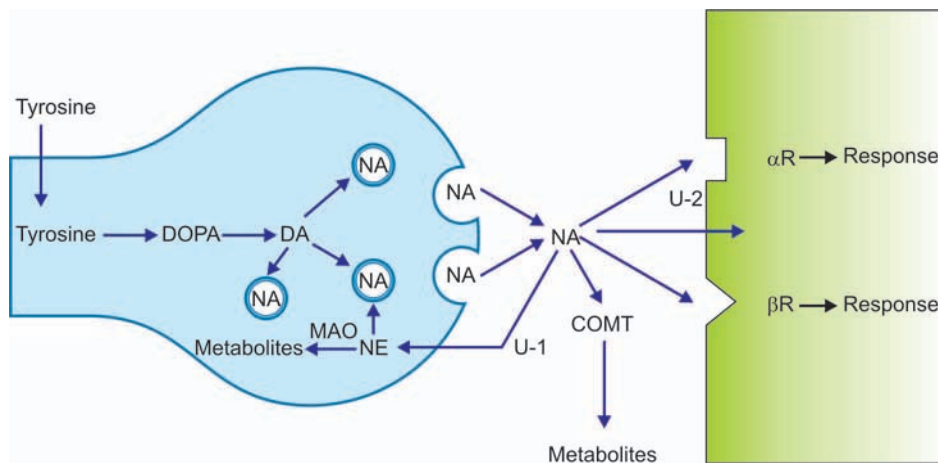


Fig. 10.2: Synthesis, storage, release and metabolism of noradrenaline

DA–Dopamine, NA–Noradrenaline, U-1–Uptake 1,
U-2–Uptake 2, MAO–Monoamine oxidase, COMT–Catechol-O-methyltransferase

membrane (Fig. 10.3). Stimulation of presynaptic α_2 receptors inhibits the further release of NA. Thus α_2 receptors exert a negative feed back on NA release. α_2

receptors are also present postsynaptically in pancreatic islets, platelets and brain.

Mechanism of action Both α and β adrenergic receptors are G-protein coupled receptors

Table 10.1: Characteristics of adrenergic receptors

Receptor type	Selective agonist	Selective antagonist	Location	Response
α_1	Phenylephrine Mephenteramine Methoxamine	Prazosin Terazosin	Vascular smooth muscle Gut Genitourinary smooth muscle Liver	Contraction Relaxation Contraction Glycogenolysis
α_2	Clonidine	Yohimbine	Pancreatic β cells Platelets Nerve terminals	$\downarrow$ Insulin release Aggregation $\downarrow$ NE release
β_1	Dobutamine	Metoprolol Atenolol	Heart	$\uparrow$ Force of contraction, $\uparrow$ heart rate, $\downarrow$ AV conduction velocity
β_2	Salbutamol	Butoxamine	Smooth muscle–vascular, bronchial, gut and genitourinary	Relaxation
β_3	—	—	Adipose tissue	Lipolysis

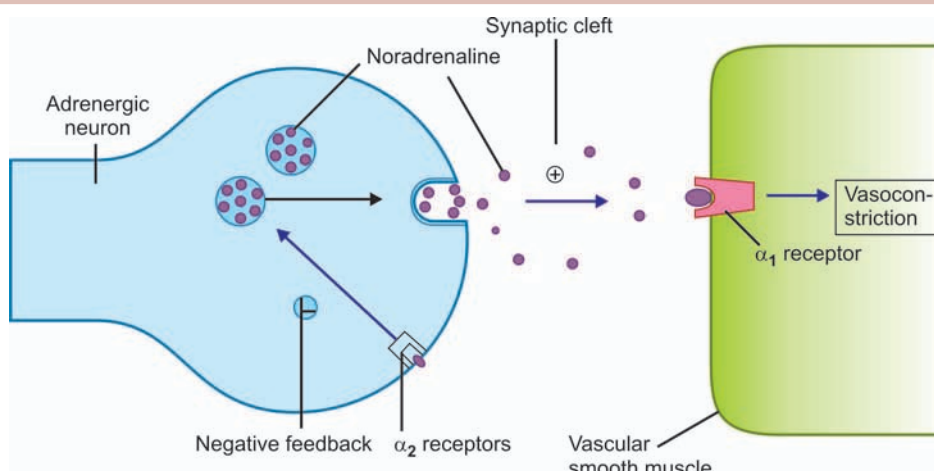


Fig. 10.3: α_1 and α_2 receptor stimulation: NA binds to α_1 receptors and stimulates it to produce response like vasoconstriction. Presynaptic α_2 receptor stimulation inhibits the further release of NA from the storage vesicles

(See page 27). Stimulation of alpha receptors activates phospholipase C in the cell membrane which acts through generation of second messengers inositol triphosphate and diacylglycerol and increase intracellular calcium.

Stimulation of beta receptors activates an enzyme adenylylcyclase resulting in increased intracellular cyclic AMP levels. This second messenger acts through various intracellular proteins to bring about the response.

Table 10.2: Compare and contrast adrenaline and noradrenaline

Feature	Adrenaline	Noradrenaline
Chemistry	Catecholamine	Catecholamine
On adrenergic receptors	Agonist	Agonist
Receptor selectivity	Both α and β	Predominantly α agonist
Effect on BP	• Biphasic • $\uparrow$ in systolic, $\downarrow$ in diastolic	• Monophasic • $\uparrow$ in systolic, diastolic and mean BP
Causes vasomotor reversal	Yes	No
Clinical uses	Many	Rarely used
Major indications	• Anaphylactic shock, • Cardiac arrest, • Local haemostatic	• Rarely used in hypotension

11

Adrenergic Drugs (Sympathomimetics)

Sympathomimetics are drugs whose actions mimic that of sympathetic stimulation. Catecholamines and sympathomimetics or adrenergic drugs may be classified in various ways depending on the presence/absence of catechol nucleus, mode of action and therapeutic indications as follows:

CLASSIFICATION

- I. *Chemical classification—based on the presence/absence of catechol nucleus*
 1. *Catecholamines*
 - Noradrenaline (NA),
 - Adrenaline,
 - Dopamine (DA),
 - Isoprenaline (Synthetic)
 2. *Non-catecholamines*
 - Ephedrine,
 - Amphetamine
- II. *Depending on the mode of action*
 1. *Directly acting sympathomimetics*
(by interacting with adrenergic receptors)
 - Noradrenaline, adrenaline,
 - dopamine, isoprenaline
 2. *Indirectly acting sympathomimetics*
(by releasing NA from nerve terminals)
 - Amphetamine, tyramine
 3. *Mixed action amines*
(both direct and indirect actions)
 - Ephedrine, methoxamine
- III. *Therapeutic or clinical classification*
 1. *Vasopressors* *Noradrenaline, dopamine, methoxamine, metaraminol*
 2. *Cardiac stimulants*
 - Adrenaline, dopamine, dobutamine,
 - isoprenaline, ephedrine
 3. *CNS stimulants*
 - Amphetamine,
 - ephedrine
 4. *Bronchodilators*
 - Adrenaline, isoprenaline, salbutamol, terbutaline, salmeterol, perbuterol, fenoterol, formoterol
 5. *Nasal decongestants*
 - Ephedrine, pseudoephedrine, phenylpropanolamine, phenylephrine, oxymetazoline, xylometazoline
 6. *Appetite suppressants*
(anorectics) *Fenfluramine, dexfenfluramine*
 7. *Uterine relaxants*
 - Salbutamol, terbutaline, isosuxuprine, ritodrine

Actions

1. *Cardiovascular System*
Heart Adrenaline is a powerful cardiac stimulant. Acting through β_1 receptors, it

increases the heart rate, force of contraction, cardiac output and conduction velocity. The work done by the heart and the resultant oxygen consumption are increased.

Blood vessels and BP Blood vessels of the skin and mucous membrane are constricted (α_1) and that of the skeletal muscles are dilated (β_2) by adrenaline. Since injection of adrenaline causes local vasoconstriction, it is used to prolong the duration of action of local anaesthetics.

Moderate doses given IV produce a rapid increase in BP followed by a fall—a biphasic response. The pressor effect is due to α_1 mediated vasoconstriction. Action on β receptors is more persistent and as the action on alpha receptors wears off, the action on β receptors gets unmasked resulting in a fall in BP. Sir Henry Dale demonstrated that when α receptors are blocked (with ergot alkaloids which are α blockers), adrenaline produces only a fall in BP and this is named after him as *Dale's vasomotor reversal* (or Dale's phenomenon).

Noradrenaline is mainly an alpha agonist and brings about a rise in BP.

Other vascular beds Adrenaline causes renal vasoconstriction resulting in a fall in renal blood flow; it also causes pulmonary and mesenteric vasoconstriction.

Cerebral and coronary blood flow is enhanced.

2. Smooth Muscles

- **Bronchi** Adrenaline is a powerful bronchodilator and a weak respiratory stimulant. Pulmonary vasoconstriction relieves bronchial congestion. All these result in an increase in vital capacity.
- **Uterus**
Nonpregnant uterus—contracts
Last month of pregnancy—relaxes.
- **Gut** Smooth muscle is relaxed—but weak and transient action.
- **Splenic capsule** contracts resulting in the release of RBCs into the circulation.

- **Pilomotor** muscles of the hair follicle contract.
- **Bladder** Detrusor is relaxed (β receptors) while trigone is contracted thereby increasing the urine holding capacity of the bladder.

3. Eye

Adrenaline causes mydriasis due to contraction of the radial muscles of the iris (α_1); it also reduces intraocular pressure.

4. Metabolic Effects

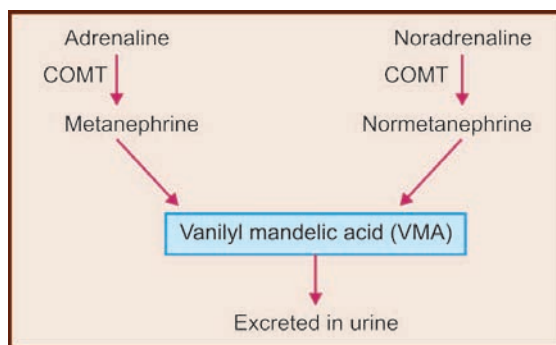
Adrenaline increases the blood sugar level by enhancing hepatic glycogenolysis. It also inhibits insulin release. By enhancing breakdown of triglycerides in the adipose tissue, more free fatty acids are made available in the plasma by action on β_3 receptors in adipocytes.

5. Skeletal Muscles

Catecholamines facilitate neuromuscular transmission by action on both α and β receptors—they enhance the amount of ACh released.

Pharmacokinetics As catecholamines are rapidly inactivated in the gut and the liver they are not given orally. Adrenaline and NA are metabolised by COMT and MAO.

Adverse reactions Anxiety, palpitation, weakness, tremors, pallor, dizziness, restlessness and throbbing headache may follow adrenaline/NA administration. In patients with ischaemic heart disease, both adrenaline



and NA can precipitate anginal pain. Rapid IV injection can cause sudden sharp rise in BP which may precipitate arrhythmias, subarachnoid haemorrhage or hemiplegia.

Preparations Adrenaline 1:1000, 1: 10,000 and 1:1,00,000 solutions are available for injection. Adrenaline is given SC/IM; intracardiac in emergencies. Adrenaline aerosol for inhalation and 2% ophthalmic solution are also available.

Uses of Adrenaline

1. *Anaphylactic shock* Adrenaline is the drug of choice (0.3-0.5 ml of 1:1000 solution). It promptly reverses hypotension, laryngeal oedema and bronchospasm and is life saving in presence of anaphylactic shock. IM route is preferred as absorption by SC route is not reliable in presence of shock. Dentists should be well versed with the use of adrenaline for this purpose because anaphylaxis can occur following the use of any drug even in dental practice.
2. *Cardiac arrest* Sudden cardiac arrest (Table 11.2) due to drowning, electrocution, etc. are treated with intracardiac adrenaline (into 4th or 5th intercostal space, 2-3 inches from the sternum); before injecting, ensure that the tip of the needle is in the heart—when the piston is withdrawn, blood should enter the syringe.
3. *Control of haemorrhage* Cotton or gauze soaked in adrenaline—1: 10,000 to 1 : 20,000 concentration is used as a topical haemostatic to control bleeding. Bleeding stops due to vasoconstriction. Adrenaline packs are used to control bleeding after tooth extraction and in epistaxis.
4. *With local anaesthetics* (see page 130) Injected with LA, adrenaline produces vasoconstriction and reduces the rate of absorption of the LA. By this it prolongs the action of the LA. It also reduces systemic toxicity of LA because as and when the LA is getting absorbed, it gets metabolised. 1: 10,000 to 1: 2,00,000 adrenaline is used for this purpose.
5. *Acute bronchial asthma* Adrenaline produces bronchodilation. It may be given SC/inhalation, but is not preferred as more selective drugs are available (See page 216).
6. *Glaucoma* (see page 49) Adrenaline ↓ IOP and can be used in glaucoma. But it has the disadvantages of being - (1) poorly absorbed, (2) short acting as it is quickly metabolised in the eye. **Dipivefrin** is a prodrug which gets converted to adrenaline in the eye by the action of corneal esterases. Dipivefrin has good penetrability due to high lipid solubility and it is used in glaucoma.

Contraindications

Adrenaline is contraindicated in patients with angina pectoris, hypertension and in patients on β blockers.

Noradrenaline can be used in shock to increase BP—but it is very rarely used.

Isoprenaline (Isoproterenol, Isopropyl arterenol) is a synthetic catecholamine with predominantly β receptor stimulant action and negligible α actions. It has cardiac stimulant and smooth muscle relaxant properties. Due to vasodilation BP falls; it is a potent bronchodilator. Adverse effects include palpitation, angina, headache and flushing.

Isoprenaline is used in heart block and shock for its cardiac stimulant actions. It can be used in bronchial asthma (page 216).

Dopamine is the precursor of NA. It acts on dopaminergic and adrenergic receptors. It is a central neurotransmitter. Low doses stimulate vascular D_1 receptors in renal, mesenteric and coronary beds causing vasodilatation in these vessels. Hence renal blood flow and GFR increase. Higher doses cause cardiac stimulation through β_1 receptors and in high doses α_1 receptors are activated

resulting in vasoconstriction and increased BP. Dopamine does not cross the BBB - hence it has no CNS effects. It is given IV (2-5 µg/Kg/min). It is short acting and the infusion rate can be adjusted to get the appropriate effect by monitoring BP. Dopamine is metabolised by COMT and MAO. **Epinine** (Ibopamine) is an ester of methyldopamine which acts like dopamine.

Adverse effects Nausea, vomiting, palpitation, headache, angina, sudden rise in BP may occur.

Uses Dopamine is used in the treatment of shock—cardiogenic, hypovolaemic and septic shock for the following reasons:

- Dopamine increases renal blood flow and thereby GFR.
- DA stimulates the heart-increases force of contraction, cardiac output and B.P. Hence it is of special value when shock is associated with renal dysfunction and low cardiac output.
- Because DA is short acting, the response can be easily controlled by modifying the infusion rate.

Dopexamine is a synthetic analog of dopamine acting on D₁ D₂ and β₂ receptors. It is found to have beneficial effects in CCF.

Dobutamine a derivative of dopamine, is a relatively selective β₁ agonist. Though it also activates α₁ receptors, in therapeutic doses the only dominant action is an increase in the force of contraction of the heart without a significant increase in the heart rate. Hence the increase in myocardial oxygen demand is milder when compared to dopamine and is therefore more useful than dopamine in cardiogenic shock. Dobutamine is used in patients with CCF or acute myocardial infarction or following cardiac surgery when there may be pump failure.

Fenoldopam is a selective D₁ agonist which dilates coronary, renal and mesenteric

arteries. It is used as an IV infusion in severe hypertension to rapidly reduce the BP.

NONCATECHOLAMINES

Noncatecholamines are devoid of catechol nucleus, they act both by direct stimulation of the adrenergic receptors and indirectly by releasing NA. In contrast to catecholamines, they are effective orally (Table 11.1), relatively resistant to MAO and therefore are longer-acting; they cross the blood-brain barrier and have CNS effects.

Ephedrine is an alkaloid obtained from the plants of the genus *Ephedra*. Ephedrine acts by direct stimulation of α and β receptors and indirectly through release of NA. Repeated administration at short intervals result in tachyphylaxis. Ephedrine raises BP by peripheral vasoconstriction and by increasing the cardiac output. Like adrenaline it relaxes smooth muscles; it is a CNS stimulant and produces insomnia, restlessness, anxiety, tremors and increased mental activity.

Adverse effects include gastric upset, insomnia, tremors and difficulty in micturition.

Uses

1. *Bronchial asthma* Ephedrine is useful in mild chronic bronchial asthma (See page 218) but it is not preferred.
2. *Nasal decongestion* Ephedrine nasal drops are used. *Pseudoephedrine*—an isomer of ephedrine is used orally for decongestion. It causes vasoconstriction in the skin and mucous membrane but its effects on the CNS and the heart are milder.
3. *Mydriasis* Ephedrine eyedrops are used to produce mydriasis without cycloplegia.
4. *Hypotension* For prevention and treatment of hypotension during spinal anaesthesia—IM ephedrine is used.
5. *Narcolepsy* is a condition with an irresistible desire and tendency to sleep. As ephedrine is a CNS stimulant, it is useful in narcolepsy.

Table 11.1: Compare and contrast noradrenaline and ephedrine

Features	Noradrenaline	Ephedrine
1. Source	Endogenous	Exogenous (From plants of genus Ephedra)
2. Chemistry	Monoamine	Non-catecholamine
3. Structure	Has catechol nucleus	No catechol nucleus
4. Mode of action	Directly stimulates adrenergic receptors	Acts both (1) directly on adrenergic receptors (2) Indirectly – through release of NA.
5. BBB	Does not easily cross	Easily crosses.
6. Action on CNS	Only in very high doses	CNS stimulation in therapeutic doses
7. Role in CNS	Central neurotransmitter	Not formed in the body.
8. Oral use	Not effective orally	Effective orally, parenterally and topically.
9. Action on adrenoceptors	Predominantly α against	Stimulates both α and β receptors.
10. $t_{1/2}$	Short (minutes)	Long (hrs)
11. Topical use	Not used	Used as eyedrops - Mydriasis Nasal drops - decongestion

6. *Nocturnal enuresis (Bed wetting)* in children may be treated with ephedrine as it increases the holding capacity of the bladder. Drugs should be used only when non-pharmacological measures have failed.

7. *Stokes Adam's syndrome* As an alternative to isoprenaline.

Amphetamine is a synthetic compound with actions similar to ephedrine; tachyphylaxis can occur on repeated use. Amphetamine is a potent CNS stimulant; it produces increased mental and physical activity, alertness, increased concentration and attention span, elation, euphoria and increased capacity to work. It also increases initiative and self confidence, postpones fatigue and improves physical performance (temporarily) as seen in athletes. All these properties make amphetamine a drug of dependence and abuse. Higher doses produce confusion, delirium and hallucinations.

Respiration Amphetamine stimulates respiration—it is an analeptic.

Depression of appetite Acting on the feeding centre in the hypothalamus, amphetamine reduces hunger and suppresses appetite.

Amphetamine also has weak anticonvulsant property.

Adverse effects include restlessness, tremors, insomnia, palpitation, anxiety, confusion and hallucinations. Prolonged use may precipitate psychosis.

High doses cause angina, delirium, arrhythmias, hypertension, acute psychosis, coma and death due to convulsions.

Dependence Amphetamine causes psychological dependence.

Uses

1. *Attention deficit hyperactivity disorder (ADHD)* in children is characterised by decreased ability to concentrate and hold attention, aggressive behaviour and hyperactivity; Amphetamine increases attention span in such children and improves performance in school.

2. *Narcolepsy* Amphetamine is preferred over ephedrine. Other drugs used in narcolepsy include *methylphenidate* and *modafinil*. Methylphenidate is an indirectly acting sympathomimetic like amphetamine. Modafinil is a centrally acting CNS stimulant which may act by stimulating α_1 adrenoceptors. It is better tolerated with fewer adverse effects.

3. *Obesity* Though appetite is suppressed, due to risk of dependence and other side effects, amphetamine should not be used for this purpose.
4. *Epilepsy* Amphetamine can be used as adjuvant and to counter the sedation due to antiepileptics.

Methamphetamine has more prominent central than peripheral actions. Methylphenidate, phenmetrazin and pemoline are other amphetamine-like drugs with actions and abuse potential similar to amphetamine.

VASOPRESSORS

These are α_1 agonists and include metaraminol, mephenteramine, phenylephrine and methoxamine. They increase the BP by increasing total peripheral resistance (TPR) or cardiac output (CO) or both. They are given parenterally with constant monitoring of BP. Tachyphylaxis may develop.

Uses Vasopressors are used to raise the BP in hypotension as seen in cardiogenic or neurogenic shock and during spinal anaesthesia.

Metaraminol is an alpha stimulant and also acts indirectly by NA release. CO is increased. It is also a nasal decongestant.

Mephenteramine acts on both α and β receptors to increase TPR and CO and thereby raises BP. It is orally effective. Pressor effect is accompanied by bradycardia.

Phenylephrine is a selective α_1 stimulant; it is also a nasal decongestant. Reflex bradycardia is prominent. It produces mydriasis without cycloplegia.

Methoxamine has actions similar to phenylephrine.

NASAL DECONGESTANTS

Nasal decongestants are α_1 agonists. They bring about vasoconstriction of the nasal

mucosa, resulting in its shrinkage and they decrease the volume of the mucosa. Thus they relieve nasal congestion and decrease resistance to airflow through the nose. They also reduce nasal secretion. The nasal decongestants thus provide symptomatic relief in rhinitis due to allergy and upper respiratory infections.

Mechanism of action - Nasal decongestants act by stimulating the α_1 receptors present in the blood vessels of the nasal mucosa.

They bring about vasoconstriction of the nasal mucosa resulting in its shrinkage. Thus they relieve nasal congestion.

They may be used:

1. *Orally* Ephedrine
Pseudoephedrine
2. *Topically (as nasal drops)*
Oxymetazoline,
Xylometazoline
Naphazoline,
Phenylephrine
Mephenteramine
Metaraminol

Adverse effects

When used orally ephedrine and pseudoephedrine can cause insomnia, tremors and irritability. On topical use, nasal irritation can occur.

Most disadvantages result from long term use - prolonged use of topical agents can cause-

- atrophy of the nasal mucosa due to intense vasoconstriction.
- reaccumulation or 'after congestion' may result when the drug is stopped (due to vasodilatation).
- loss of efficacy or tolerance due to desensitization of the receptors.

Nasal decongestants should be used carefully in patients with hypertension. The use of phenylpropanolamine is associated with an increased risk of haemorrhagic stroke and is therefore **banned**.

Uses

- Rhinitis in upper respiratory infections.
- Allergic and vasomotor rhinitis, sinusitis.
- Blocked eustachian tubes.

Nasal decongestants afford symptomatic relief in the above conditions.

SELECTIVE β_2 STIMULANTS

Selective β_2 stimulants include orciprenaline, salbutamol, terbutaline and the newer ones include salmeterol, perbuterol, bitolterol, fenoterol and formoterol. These are smooth muscle relaxants which produce broncho-dilatation, vasodilation and uterine relaxation without significant cardiac stimulation. Salbutamol and other β_2 stimulants can be given by inhalation.

Side effects include muscle tremors, palpitation and arrhythmias.

Uses

- Bronchial asthma (chap 32)
- As uterine relaxants to delay *premature labour*.

Isosuxuprine is a selective β receptor stimulant used as uterine relaxant in premature labour, threatened abortion and dysmenorrhoea.

ANORECTIC AGENTS (ANOREXIANTS)

Though *amphetamine* suppresses appetite, it is not recommended for the treatment of obesity due to its central stimulant effects. Many amphetamine like drugs which suppress appetite but lack significant CNS stimulant effects are now available. They are *fenfluramine*, *dexfenfluramine*, *mazindol*, *phenylpropanolamine* (now banned), *penmetrazine* and others. *Adverse effects* include risk of abuse, drowsiness and depression because of which they are only used for short periods as adjuncts to other measures.

Sibutramine suppresses appetite and has been tried in obesity. It inhibits the uptake of NA and 5-HT but causes many serious adverse effects including insomnia, anxiety, mood changes, hypertension and cardiovascular deaths.

Table 11.2 : Uses of adrenergic agonists

<i>Indication</i>	<i>Sympathomimetics used</i>
1. Cardiac arrest	– Adrenaline
2. Hypotension	– Methoxamine, mephenteramine
3. Hypertension	– Clonidine (α_2 agonist)
4. Anaphylactic shock	– Adrenaline
5. Severe allergic reactions (bee sting, food & drug allergy)	– Adrenaline
6. To arrest local bleeding	– Adrenaline
7. To prolong local anaesthesia	– Adrenaline
8. Bronchial asthma	– Salbutamol, terbutaline, salmeterol, ibutanol
9. Narcolepsy	– Amphetamine, ephedrine
10. Glaucoma	– Adrenaline, dipivefrine
11. Weight reduction	– Fenfluramine, dexfenfluramine, mazindol, amphetamine
12. Nasal decongestion	– Oxymetazoline, xylometazoline,
13. Mydriasis for funduscopy	– Phenylephrine
14. Attention deficit hyperactivity disorder	– Amphetamine, methylphenidate

12

Adrenergic Antagonists

Adrenergic blockers bind to the adrenergic receptors and prevent the action of adrenergic drugs. They may block alpha or beta receptors or both.

ALPHA ADRENERGIC BLOCKING AGENTS

Alpha receptor antagonists block the adrenergic responses mediated through alpha adrenergic receptors. Some of them have selectivity for α_1 or α_2 receptors.

Actions

The important effects of α receptor stimulation are α_1 mediated vasoconstriction and α_2 - (presynaptic) receptor mediated inhibition of NA release. The result of alpha blockade by α -antagonists (Fig 10.3, Page 68) are:

α_1 -blockade—inhibits vasoconstriction -- leading to vasodilation and thereby $\downarrow$ BP. This fall in BP is opposed by the baroreceptor reflexes which tend to $\uparrow$ heart rate and cardiac output.

α_2 -blockade—enhances release of NA which stimulates β receptors (α are already blocked) - β_1 stimulation in heart results in tachycardia and increased cardiac output.

Thus the predominant effects of non-selective α -blockade is hypotension with tachycardia. This is because α_2 receptors are blocked and there is no increase in NA release.

Selective α_1 -blockade—results in hypotension without significant tachycardia.

Selective α_2 -blockade— $\uparrow$ NA release resulting in hypertension.

α -blockade also results in miosis and nasal stuffiness. α -blockade in the bladder and prostate leads to decreased resistance to the flow of urine.

Adverse effects of α -blockers—Postural hypotension, palpitation, nasal stuffiness, miosis, impaired ejaculation and impotence. α blockers are classified as follows—

1. Non-selective

a. Non-competitive blocker

Phenoxybenzamine

b. Competitive blockers

Ergot alkaloids (ergotamine), tolazoline, phentolamine, chlorpromazine

2. Selective

a. α_1 -blockers

Prazosin, terazosin, doxazosin, tamsulosin, alfuzosin

b. α_2 -blocker

Yohimbine

Phenoxybenzamine binds covalently to alpha receptors causing irreversible blockade. Given IV, blood pressure gradually falls and is associated with tachycardia and increased CO. The action lasts for 3-4 days. It also blocks histamine, 5-HT and cholinergic receptors. Phenoxybenzamine can be used orally in the treatment of pheochromocytoma (Table 12.1).

Ergot alkaloids (Page 208) Ergotamine, ergotamine and their derivatives are competitive antagonists and the blockade is

of short duration. Some of them have a direct stimulant effect on smooth muscles—cause contraction of the uterus and $\uparrow$ BP due to vasoconstriction. Prolonged use of these can cause gangrene of the toes and fingers.

Phentolamine and tolazoline are competitive α -blockers. In addition they also block 5-HT receptors, stimulate gut motility and $\uparrow$ gastric secretion. Hence they can cause vomiting and diarrhoea in addition to the effects of α -blockade.

Selective α_1 Blockers

Prazosin is a potent, highly selective, α_1 -blocker with 1000 times greater affinity for α_1 receptors. Arterioles and venules are dilated resulting in decreased peripheral vascular resistance and cardiac output (CO falls because of venodilation $\rightarrow$ decreased preload). There is no significant tachycardia (as α_2 receptors are spared there is no $\uparrow$ in NA release). In addition it may decrease central sympathetic outflow. Prazosin also inhibits phosphodiesterase, the enzyme that degrades cAMP resulting in $\uparrow$ cAMP which also contributes to vasodilation.

Other actions:

- Prazosin and its congeners are found to $\downarrow$ LDL and triglycerides and $\uparrow$ HDL cholesterol.

- They also relax the urinary bladder neck and the prostatic capsule because of which they are useful in prostatic hypertrophy.

Prazosin is orally effective, extensively bound to plasma proteins and is metabolised in the liver. Its duration of action is 8-10 hrs. *Adverse effects* First dose phenomenon— one hour after the initial dose, marked postural hypotension occurs which may lead to fainting. To avoid this, prazosin should be started with a low dose and taken at bed time. Other side effects include headache and dizziness. Tamsulosin can cause abnormal ejaculation.

Congeners of Prazosin—include terazosin, doxazosin, alfuzosin and tamsulosin. Others are indoramin and urapidil.

- These congeners are longer acting and can be given once daily.
- highly selective for α_1 receptors.
- Postural hypotension is milder than with prazosin.
- No significant effect on cardiac function.
- $\downarrow$ LDL and $\uparrow$ HDL cholesterol
- Tamsulosin has selective activity on α_{1A} receptors in the bladder and prostate while hypotension (mediated by α_{1B}) is mild. Therefore tamsulosin relieves the symptoms of benign prostatic hypertrophy (BPH) and is used in BPH.

Table 12.1 Compare and contrast phenoxybenzamine and prazosin

Features	Phenoxybenzamine	Prazosin
Chemistry	β haloalkylamine	Quinazoline
Receptors blocked	α adrenergic	α adrenergic
Receptor Subtype Selectivity	Both α_1 and α_2	α_1 selective
Type of blockade	Non equilibrium	Equilibrium
Effects of α_2 blockade	$\uparrow$ NA release	Does not increase
Reflex tachycardia	Significant	Negligible
Postural hypotension	Significant	Less
Primary use	Pheochromocytoma	Hypertension

- Alfuzosin is also useful in BPH.
- Terazosin and doxazosin are used in hypertension.
- Urapidil has α_1 and β_1 (weak) blocking properties. It is used in hypertension and BPH.

Yohimbine is a relatively selective α_2 -blocker which increases BP and heart rate due to $\uparrow$ NA release. It causes congestion of genitals because of which it is used to treat psychogenic impotence. It is also claimed to be an aphrodisiac though the effect is only psychological.

Uses of α -blockers

1. *Hypertension* Selective α_1 -blockers like prazosin are used in the treatment of hypertension (Page 116). Phenoxybenzamine or phentolamine can be used in hypertensive crisis.
2. *Pheochromocytoma* is an adrenal medullary tumour which secretes large amounts of catecholamines resulting in hypertension. The tumour has to be removed surgically. Phenoxybenzamine and phentolamine are used for the preoperative management of the patient and during the operation. Inoperable cases are put on long-term treatment with phenoxybenzamine.
3. *Peripheral vascular diseases* like Raynaud's phenomenon may be benefited by α -blockers which afford symptomatic relief.
4. *Congestive cardiac failure* Because of its vasodilator action, prazosin is useful in CCF. But ACE inhibitors are preferred.
5. *Benign prostatic hypertrophy (BPH)* Blockade of α_1 receptors in the bladder, prostate and urethra reduce resistance to urine outflow. Prazosin, tamsulosin and alfuzosin are useful in patients who cannot be operated upon.

BETA ADRENERGIC BLOCKING AGENTS

β -blockers are drugs that block the actions of catecholamines mediated through the β receptors.

Classification

1. *Non-selective:*
Propranolol, nadolol
timolol, sotalol
2. *Cardioselective (β_1)*
Metoprolol, atenolol,
acebutolol, esmolol
3. *Partial agonists*
Pindolol, oxprenolol,
carteolol, bopindolol,
penbutolol
4. *With additional alpha blocking property*
Labetalol, carvedilol
5. *β_1 blocker β_2 agonist*
Celiprolol.

Pharmacological Actions

1. *CVS* β -blockers decrease heart rate, force of contraction and cardiac output. Blood pressure falls. The effect is more pronounced in presence of increased sympathetic tone than in a normal situation. AV conduction is delayed. Myocardial oxygen requirement is reduced due to reduced cardiac work. They also improve exercise tolerance in angina patients. β -blockers prevent the exercise-induced increase in heart rate and force of contraction.
High doses cause direct depression of the heart.
2. *Respiratory tract* Blockade of β_2 receptors in the bronchial smooth muscle causes increase in airway resistance—may precipitate acute attack in asthmatics.
3. *Eye* Many β -blockers reduce intraocular pressure by decreased secretion of aqueous humor.

4. *Metabolic* β -antagonists block lipolysis and glycogenolysis (β_2 mediated) induced by sympathetic stimulation. Hence non-selective β blockers may interfere with recovery from hypoglycaemia in diabetics. Plasma triglycerides may increase and HDL levels decrease in some patients.

Pharmacokinetics

Though well absorbed on oral administration, some β -blockers like propranolol undergo extensive first pass metabolism. Most of them have short $t_{1/2}$ and are metabolised in the liver. Dose Table 12.3

Adverse Reactions

1. *Bradycardia* is common. Patients with AV conduction defects may develop arrhythmias and heart block with β -blockers.
2. *CCF* In patients with impaired myocardial function, sympathetic activity supports the heart. β -blockade eliminates this and may precipitate CCF and acute pulmonary edema.
3. *Cold extremities* may be experienced

especially in patients with peripheral vascular disease.

4. β -blockers can precipitate *acute asthmatic attack* in asthmatics and is contraindicated in them.
5. *CNS* Insomnia, depression and rarely hallucinations can follow the use of β -blockers.
6. *Fatigue* due to decreased blood flow to the muscles during exercise and reduced cardiac output.
7. *Metabolic effects* Weakness, $\downarrow$ exercise capacity may be seen due to its metabolic effects.
8. Abrupt withdrawal of β -blockers after prolonged use can cause *rebound hypertension* and precipitate anginal attacks. This is due to up-regulation of β receptors. Hence β -blockers should be gradually tapered.
9. β blockers can also cause *dizziness*.

Contraindications

Beta blockers are contraindicated in bradycardia, heart block, asthmatics and chronic obstructive pulmonary disease (COPD).

Table 12.2: Compare and contrast propranolol and atenolol

Features	Propranolol	Atenolol
1. Receptors blocked	Both β_1 and β_2	β_1 selective
2. Lipid solubility	High	Low
3. First pass metabolism	High	Not significant
4. Protein binding	Extensive (>90%)	Poor (<5%)
5. BBB	Crosses	Does not cross
6. Effects on CNS	Significant	No significant effects
7. Excretion through kidneys	Negligible (0.5%)	Major route (85%)
8. Plasma $t_{1/2}$	3 – 6 hrs	6 – 8 hrs
9. Duration of action	Short (6-12 hrs)	Long (12 – 24 hrs)
10. In asthmatic and chronic bronchitis patients	Contraindicated	Not contraindicated - used with caution
11. In diabetics and peripheral vascular diseases	Avoided	Can be used with caution
12. Local anaesthetic action	Yes	No

Some Important Drug Interactions

1. Propranolol + insulin—when diabetics on insulin also receive propranolol:
 - i. β -blockade masks tachycardia which is the first warning signal of hypoglycaemia.
 - ii. β -blockade delays the recovery from hypoglycaemia by preventing glycogenolysis induced by sympathetic stimulation (acting through β_2 receptors). This may be avoided by using a β_1 selective blocker.
2. Propranolol + verapamil—Because both these cause myocardial depression, profound depression may result if both are used together. Hence the combination should be avoided.
3. β -blockers + catecholamines—in patients on nonselective β -blockers, blockade of vascular β receptors results in up regulation of the receptors and intense vasoconstriction is possible from even small doses of adrenaline that is used with LAs. Hence it is safer to use plain local anaesthesia in such patients.

Cardioselective β -blockers e.g. Atenolol, metoprolol, esmolol.

These drugs:

- Selectively block β_1 receptors; β_2 -blockade is weak
- Bronchospasm is less/negligible
- Inhibition of glycogenolysis is lower—hence safer in diabetics
- Exercise performance is impaired to a lesser degree
- Lesser chances of peripheral vascular disease.

Partial agonists—Pindolol, oxprenolol.

These have some sympathomimetic activity due to their partial β -agonistic property. As a result, bradycardia and myocardial depression are less marked. They are therefore preferred in patients who are likely to have severe bradycardia.

Some Individual β -antagonists

Atenolol (see Table 12.2)

- Selective β_1 -blocker
- Longer acting—given once daily
- Less lipid soluble—does not cross BBB—hence no CNS side effects
- No side effects on lipid profile. Hence very commonly used (25–100 mg daily)

Esmolol

- Selective β_1 -blocker
- Ultra short-acting— $t_{1/2}$ —8 minutes.
- Used IV
- Safer in critically ill patients and in emergencies when immediate β -blockade is needed.

Metoprolol

- Selective β_1 blocker
- Well absorbed but undergoes significant first-pass metabolism
- Given twice daily (50–200 mg)
- Used in hypertension and angina pectoris

Acebutolol

- β_1 selective with some partial agonistic effects
- May be used in hypertension and arrhythmias.

Celiprolol

- β_1 blocker and β_2 agonistic effects
- Safer in asthmatics
- Used in hypertension.

Timolol

- Nonselective, short-acting
- Used in glaucoma—as eyedrops.

Uses of β -blockers

1. *Hypertension* β -blockers are useful in the treatment of mild to moderate hyper-

Table 12.3: Doses of some β -blockers

Drug (Trade name)	Total daily dose (mg)	Frequency
Propranolol (INDERAL)	40-240	6-12 hr
Metoprolol (MEFOCARD)	50-200	12-24 hr
Atenolol (ATEN)	25-100	once daily
Pindolol (PINADOL)	10-45	6 hr
Acebutolol (SECTRAL)	200-400	12-24 hr

- tension. A β -blocker can be used alone or with other antihypertensives (Page 116).
2. *Angina pectoris* β -blockers are useful in the prophylaxis of exertional angina. Both the severity and frequency are reduced (page 106). They reduce both cardiac work and O_2 demand.
 3. *Cardiac arrhythmias* β -blockers are useful in the treatment of both ventricular and supraventricular arrhythmias. Sotalol has additional antiarrhythmic effects (Page 102).
 4. *Myocardial infarction* IV β -blockers in acute MI may limit the size of the infarct. In patients who have recovered from MI, long-term treatment with β -blockers prolongs survival (page 108).
 5. *Congestive cardiac failure* Earlier experience has shown that β -blockers can worsen CCF because of their negative inotropic effect (page 95). But several recent studies have shown that when judiciously used in selected patients, β blockers can be beneficial in CCF. They reduce the risk of sudden death and prolong survival on long term use. The exact mechanism is not known. Sympathetic system is stimulated in CCF which may in fact be deleterious to the heart in many ways and even contribute to cardiac remodelling. Blocking the β receptors may help to improve cardiac function and prevent cardiac remodelling.
 6. *Obstructive cardiomyopathy* β -blockers are found to be beneficial.
 7. *Pheochromocytoma* Propranolol is given with α -blockers before surgery to control hypertension.
 8. *Thyrotoxicosis* Propranolol controls palpitation, tremors and affords symptomatic relief in thyrotoxicosis; it is used as an adjuvant. It is also useful in thyrotoxic crisis.
 9. *Glaucoma* Timolol is used topically in open angle glaucoma. Newer β -blockers are now developed.
 10. *Prophylaxis of migraine* Propranolol reduces the frequency and severity of migraine headache; used for prophylaxis.
 11. *Anxiety* Propranolol prevents the acute panic symptoms seen in public speaking, examination and other such anxiety-provoking situations. Performance in musicians can be improved. Tremors, tachycardia and other symptoms of sympathetic overactivity are alleviated.

Alpha and Beta-adrenergic Blockers

Labetalol blocks both α_1 and β (β_1 and β_2) receptors. It is a competitive antagonist. Heart rate, contractility, AV conduction and BP fall. Vasodilation (α_1 and β blockade) and reduced CO contribute to antihypertensive effect. Blood flow to the limbs increases.

Side effects include postural hypotension, GI disturbances and other effects of alpha and beta blockade.

Uses Labetalol is used in hypertensive emergencies and pheochromocytoma.

Carvedilol and medroxalol also are alpha and β -antagonists. Carvedilol blocks α_1 , β_1 and β_2 receptors. In addition it has antioxidant property. It is used in the treatment of hypertension and congestive cardiac failure.

Section 3

Drugs Acting on the Kidney

13

Diuretics and Antidiuretics

Kidney, the excretory organ of our body serves the important functions of excretion of waste products, regulation of fluid volume and electrolyte content of the extracellular fluid.

PHYSIOLOGY OF URINE FORMATION

Normally about 180 litres of fluid is filtered everyday, of which 99% gets reabsorbed and about 1.5 litres of urine is formed. For simplification, the nephron can be divided into four sites (Fig. 13.1).

Proximal tubule Sodium bicarbonate, sodium chloride, amino acids and glucose are reabsorbed in the proximal tubule along with water by specific transport mechanisms. Osmotic diuretics act here.

Henle's loop In the thin descending limb of the loop of Henle, water is reabsorbed by osmotic forces. Hence osmotic diuretics are acting here too. The thick ascending limb actively reabsorbs sodium chloride from the lumen (but is impermeable to water) by $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ co-transporter. 'Loop diuretics' selectively block this transporter.

Distal convoluted tubule In the early distal tubule, sodium chloride is reabsorbed by an electrically neutral Na^+ and Cl^- transporter. This transporter is blocked by thiazide diuretics.

Collecting tubule In the late distal tubule and collecting duct, NaCl is actively reabsorbed,

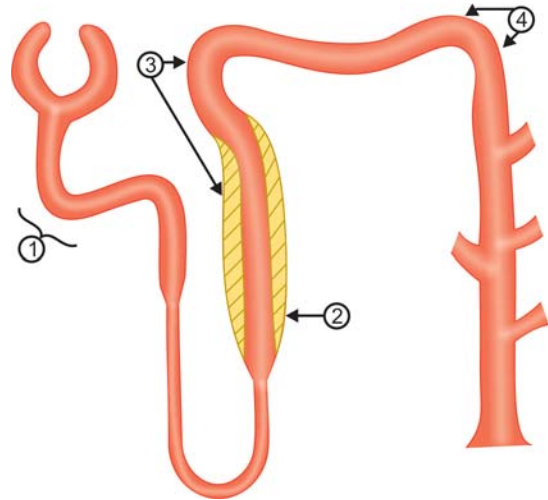


Fig. 13.1: Simplified diagram of a nephron showing sites of action of diuretics (1) Proximal tubule—osmotic diuretics, mannitol, (2) Ascending limb of Henle's loop—loop diuretics, (3) Early distal tubule—thiazides, (4) Distal tubule and collecting duct— K^+ sparing diuretics

in exchange for K^+ and H^+ to maintain the ionic balance regulated by aldosterone. Absorption of water is under the control of antidiuretic hormone (ADH).

Diuretic is an agent which increases urine and solute excretion. Diuretics may be classified as follows-

CLASSIFICATION

1. High efficacy diuretics

Furosemide, bumetanide, piretanide, ethacrynic acid, torsemide, azosemide

2. *Moderate efficacy diuretics***Thiazides**

Benzothiadiazines—Chlorothiazide, hydrochlorothiazide, polythiazide, bendroflumethiazide, Cyclopenthiiazide

Thiazide related agents

Chlorthalidone, clopamide, indapamide, metolazone, xipamide

3. *Low efficacy diuretics**Potassium sparing diuretics*

Triamterene, amiloride, spironolactone

Carbonic anhydrase inhibitors

Acetazolamide, methazolamide, dorzolamide

Osmotic diuretics

Mannitol, urea, glycerol

Methylxanthines

Theophylline

HIGH EFFICACY, HIGH CEILING OR LOOP DIURETICS

Loop diuretics act on the ascending limb of the loop of Henle. They are highly efficacious as diuretics. Frusemide is the most commonly used loop diuretic.

Frusemide (Furosemide) is a sulfonamide derivative. It is a powerful diuretic.

Mechanism of Action

Frusemide acts by inhibiting NaCl -reabsorption in the thick ascending limb of the Henle's loop (Fig. 13.2). It blocks the $\text{Na}^+ \text{K}^+ 2\text{Cl}^-$ symporter in the thick ascending limb of the Henle's loop because of which it is called is a loop diuretic. It greatly increases the excretion of Na^+ and Cl^- in the urine. As a large amount of NaCl is absorbed in this segment, loop diuretics are highly efficacious. Diuretic response increases with dose and over-enthusiastic treatment can cause dehydration (high ceiling of effect) (Table 13.1).

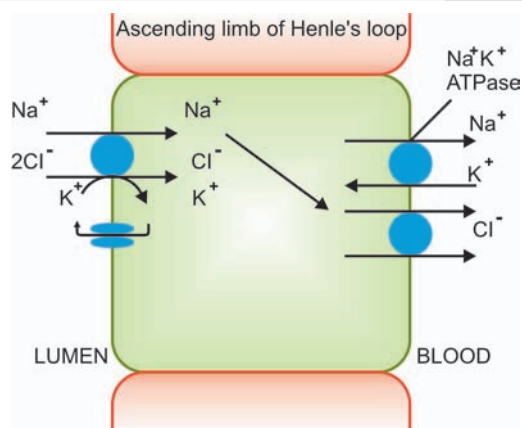


Fig 13.2: Mechanism of action of loop diuretics

Other actions Loop diuretics also enhance the excretion of K^+ , Ca^{++} and Mg^{++} (but Ca^{++} is reabsorbed in the distal tubule—hence no hypocalcaemia). They increase reabsorption of uric acid in the proximal tubule. On long term use, they also alter renal haemodynamics to reduce fluid and electrolyte reabsorption in the proximal tubule. Frusemide is also a weak carbonic anhydrase inhibitor hence it increases the excretion of HCO_3^- and phosphate. Loop diuretics enhance renin release.

Given intravenously frusemide acts in 2-5 minutes, while following oral use, it takes 20-40 minutes; duration of action is 3-6 hours.

Intravenous frusemide causes venodilation and reduces left ventricular filling pressure. It thus relieves pulmonary congestion in congestive heart failure and in pulmonary edema even before the onset of diuresis.

Pharmacokinetics Furosemide is rapidly absorbed orally, (Table 13.3) highly bound to plasma proteins, metabolised in the liver and excreted by kidneys. Plasma $t_{1/2}$ is 1½ hours and duration of action is 4 to 6 hours. Loop diuretics reach the ascending limb of

Henle's loop as they are secreted by the organic acid transport system.

Bumetanide is a sulfonamide like frusemide but is 40 times more potent than frusemide. Bioavailability is 80% and is better tolerated. *Ethacrynic acid* is more likely to cause adverse effects and hence is not commonly used.

Torsemide is a recently introduced loop diuretic. It is longer acting and therefore can be given once a day.

Adverse Effects of Loop Diuretics

1. *Hypokalaemia and metabolic alkalosis* (due to loss of H^+) is dose dependent and can be corrected by K^+ replacement and correction of hypovolaemia.
2. *Hyponatraemia, dehydration hypovolaemia and hypotension* should be treated with saline infusion.
3. *Hyperuricaemia* may precipitate acute attacks of gout.
4. *Hypocalcaemia and hypomagnesaemia* - After prolonged use this may result in osteoporosis.
5. *Ototoxicity* Loop diuretics cause hearing loss by a toxic effect on the hair cells in the internal ear. Associated tinnitus and vertigo may also occur. Ototoxicity is more common with ethacrynic acid. It is dose-related, more common on IV administration and generally reversible. Concurrent use of other ototoxic drugs should be avoided.
6. *Hyperglycaemia and hyperlipidaemia* are mild in therapeutic doses.
7. *GIT disturbances* like nausea, vomiting and diarrhoea are common with ethacrynic acid.
8. *Allergic reactions* like skin rashes are more common with sulfonamide derivatives.

Uses

1. *Edema* Loop diuretics are highly effective for the relief of edema of all origins like cardiac, hepatic or renal edema. In chronic congestive cardiac failure loop diuretics reduce venous and pulmonary congestion.
2. *Acute pulmonary edema* is quickly relieved by IV frusemide due to its immediate vasodilator effect and then by diuretic action.
3. *Cerebral edema*- frusemide is used as an alternative to osmotic diuretics.
4. *Forced diuresis* In poisoning due to drugs like barbiturates and salicylates, frusemide is used with IV fluids.
5. *Hypertension* with renal impairment may be treated with loop diuretics.
6. *Hypercalcaemia and hyperkalaemia* Loop diuretics enhance excretion of Ca^{++} and K^+ . But Na^+ and Cl^- should be replaced to avoid hyponatraemia and hypochloroemia.

THIAZIDES AND THIAZIDE-LIKE DIURETICS

Chlorothiazide was the first thiazide to be synthesized. All thiazides have a sulfonamide group.

Actions and Mechanism of Action

Thiazides act on the early distal tubule. Thiazides have a moderate efficacy because 90% of the filtered sodium is already reabsorbed before reaching the distal tubule. This group of drugs block Na^+/Cl^- co-transport system (Fig. 13.3) in the early distal tubule (site 3). They also inhibit carbonic anhydrase activity and increase bicarbonate loss. Thiazides also enhance excretion of Mg^{++} .

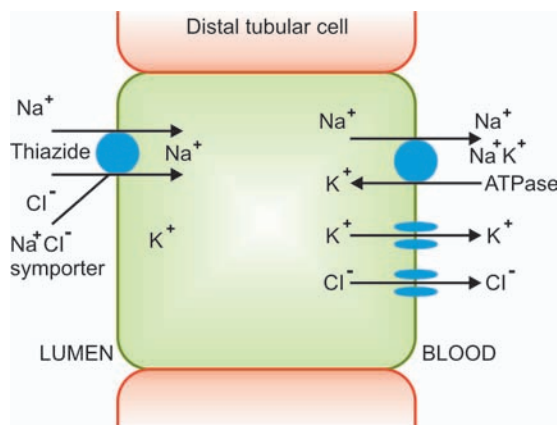


Fig. 13.3: Mechanism of action of thiazide diuretics

and K^+ (in distal segments, Na^+ in the lumen is exchanged for K^+ which is then excreted). But they inhibit urinary excretion of Ca^{++} and uric acid resulting in hypercalcaemia and hyperuricaemia.

Pharmacokinetics

Thiazides are well absorbed orally and are rapid acting. Duration varies from 6-48 hr (Table 13.2). They are excreted by the kidney.

Adverse Effects

Hypokalaemia, metabolic alkalosis, hyperuricaemia, hypovolaemia, hypotension, dehydration, hyponatraemia, hypomagnesaemia, hypochloraemia, hypercalcaemia, and hyperlipidaemia are similar to that seen with loop diuretics. Hyperglycaemia induced by thiazides may precipitate diabetes mellitus probably by inhibition of insulin secretion. It is more common when long-acting thiazides are used for a long time. Thiazides can cause impotence in men. Weakness, fatigue, anorexia, gastrointestinal disturbances and allergic reactions like rashes and photosensitivity can be seen.

Uses

1. *Hypertension* Thiazides are the first line drugs (see page 111).
2. *Congestive heart failure* Thiazides are useful in the management of edema due to mild to moderate CHF.
3. *Edema* Thiazides may be tried in hepatic (cirrhosis) or renal edema. Renal edema may be due to nephrotic syndrome, acute glomerulonephritis or chronic renal

Table 13.1: Compare and contrast hydrochlorothiazide and frusemide

Features	Hydrochlorothiazide	Frusemide
Efficacy	Low	High
Site of action	Early distal tubule	Ascending limb of loop of Henle
Mechanism of action	Inhibits Na^+Cl^- symport	Inhibits $Na^+K^+2Cl^-$ cotransport
Onset of action	After 1 hour	In minutes (20-40)
Duration action	Long (8-12 hrs)	Short (3-6 hrs)
Response to increasing dose	No significant increase	Increases (Dose dependent)
Hyperuricemia	Higher incidence	Low
Blood glucose	May increase – Contraindicated in Diabetics	No significant effect Not contraindicated
Ototoxicity	Not known to cause	Can cause
Primary use	Hypertension	Edema

Table 13.2: Dose and duration of action of commonly used diuretics

Diuretic	Daily dose (mg)	Duration (hrs)	Brand name
Furosemide	20-80 mg	3-6	LASIX
Bumetanide	0.5-2 mg	3-6	BUMET
Hydrochlorothiazide	25-100	8-12	ESIDREX
Polythiazide	1-3	24-48	NEPHRIL
Chlorthalidone	50-100	48-72	HYTHALTON
Xipamide	20-60	24-36	XIPAMID
Metolazone	5-10	18-24	ZAROXYLIN
Spironolactone	50-100	6-12	ALDACTONE
Triamterene	50-100	4-6	DYTIDE (with benzthiazide)
Amiloride	5-10	20-24	LASIRIDE (with frusemide)

failure. Metolazone may be combined with loop diuretics in severe refractory edema.

4. *Renal stones* Hypercalciuria with renal stones can be treated with thiazides which reduce calcium excretion.
5. *Diabetes insipidus* Thiazides reduce plasma volume and GFR - a paradoxical effect - and benefit such patients.

Indapamide is particularly suitable in hypertension because it is claimed to lower blood pressure in subdiuretic doses and in such doses adverse effects are milder. It is well absorbed orally and has a long duration of action to permit once a day dosing.

POTASSIUM SPARING DIURETICS

Aldosterone enhances the Na^+ reabsorption through Na^+ channels in the collecting tubule and enhances K^+ secretion. It binds aldosterone receptors on distal tubule and collecting duct and competitively inhibits the action of aldosterone. *Spironolactone* is an aldosterone antagonist (Fig. 13.4). As major amount of Na^+ is already reabsorbed in the proximal parts, spironolactone has low efficacy. Spironolactone also reduces K^+ loss due to other diuretics.

It enhances the excretion of calcium by a direct action on the renal tubules.

Adverse effects include gynaecomastia, drowsiness, hyperkalaemia especially in renal insufficiency; metabolic acidosis and skin rashes.

Amiloride and *triamterene* are directly acting agents which enhance Na^+ excretion and

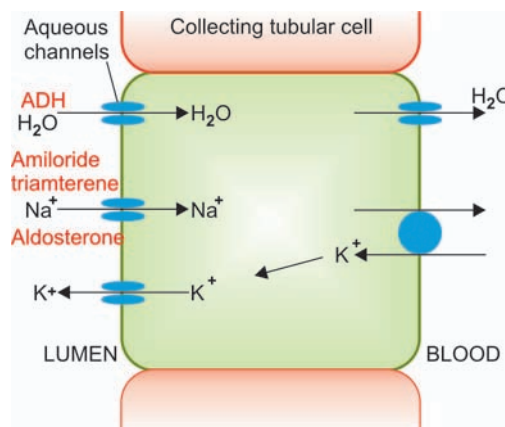


Fig 13.4: Mechanism of action of potassium sparing diuretics. Spironolactone antagonises the action of aldosterone while amiloride and triamterene directly inhibit the Na^+ channels. (ADH promotes reabsorption of water through aqueous channels - it also increases the number of these channels).

Table 13.3: Compare and contrast frusemide and spironolactone

Features	Frusemide	Spironolactone
Chemistry	Sulfonamide	Synthetic steroid
Sites of action	Ascending limb of loop of Henle	Distal tubule and collecting duct
Mechanism of action	Blocks $\text{Na}^+/\text{K}^+ / 2 \text{Cl}$ cotransport	Aldosterone antagonist
Efficacy	High	Low
Onset of action	Quick - 2-5 minutes	Slow – May take several days
Effect on K^+	$\uparrow$ Excretion – Hypokalaemia	$\downarrow$ excretion – Hyperkalaemia
Unique adverse effects	Ototoxicity	Gynaecomastia, Hirsutism
Primary use	* CCF, edema, ascitis * Pulmonary edema	* Hyperaldosteronism * As adjuvant to other diuretics to reduce K^+ loss.
Contraindications	Allergy to sulfonamides	Peptic ulcer

reduce K^+ loss by acting on ion channels in the distal tubule and collecting duct. They block the Na^+ transport through ion-channels in the luminal membrane. Since K^+ secretion is dependent on Na^+ entry, these drugs reduce K^+ excretion.

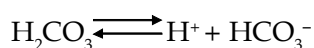
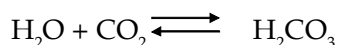
Adverse effects are gastrointestinal disturbances, hyperkalaemia and metabolic acidosis.

Uses of K^+ Sparing Diuretics

1. *With thiazides and loop diuretics* to prevent potassium loss.
2. *Edema* In cirrhosis and renal edema where aldosterone levels may be high.
3. *Hypertension* Along with thiazides to avoid hypokalaemia and for additive effect.
4. *Primary or secondary aldosteronism* Spironolactone is used.

CARBONIC ANHYDRASE INHIBITORS

Carbonic anhydrase is an enzyme that catalyses the formation of carbonic acid which spontaneously ionises to H^+ and HCO_3^- . This HCO_3^- combines with Na^+ and is reabsorbed.



Carbonic anhydrase inhibitors block sodium bicarbonate reabsorption and cause HCO_3^- diuresis. Carbonic anhydrase is present in the nephron, eyes, gastric mucosa, pancreas and other sites.

Acetazolamide, a sulfonamide derivative is a carbonic anhydrase inhibitor and enhances excretion of sodium, potassium, bicarbonate and water. The loss of bicarbonate leads to metabolic acidosis.

Other Actions

1. *Eye* The ciliary body of the eye secretes bicarbonate into the aqueous humor. Carbonic anhydrase inhibition results in decreased formation of aqueous humor and thereby reduces intraocular pressure.
2. *Brain* Bicarbonate is secreted into CSF and carbonic anhydrase inhibition reduces the formation of CSF.

Adverse Effects

1. Metabolic acidosis due to HCO_3^- loss.
2. Renal stones— Ca^{++} is lost with HCO_3^- resulting in hypercalciuria. This excess Ca^{++} may precipitate resulting in the formation of renal stones.

3. Hypokalaemia, drowsiness and allergic reactions can occur.

Uses

1. Glaucoma—(see page 49) Intraocular pressure is decreased by acetazolamide; it is given orally. Newer ones—*methazolamide* and *dorzolamide* are better tolerated and are available as eye drops.
2. Alkalinization of urine—as required in overdosage of acidic drugs. Also, uric acid and cysteine excretion can be enhanced as these are soluble in alkaline urine.
3. Metabolic alkalosis—acetazolamide enhances HCO_3^- excretion.
4. Mountain sickness—In mountain climbers who rapidly ascend great heights, severe pulmonary edema or cerebral edema may occur. Acetazolamide may relieve symptoms by reducing the formation and pH of CSF—it can also be used for prophylaxis.
5. Epilepsy—acetazolamide is used as an adjuvant as it increases the seizure threshold.

OSMOTIC DIURETICS

Mannitol is a pharmacologically inert substance. When given IV (orally not absorbed), mannitol gets filtered by the glomerulus but not reabsorbed. It causes water to be retained in the proximal tubule and descending limb of Henle's loop by osmotic effect resulting in water diuresis. There is also some loss of sodium.

Adverse effects are dehydration, ECF volume expansion, headache and allergic reactions.

Uses

1. To maintain urine volume and prevent oliguria in conditions like massive haemolysis and shock.

2. To reduce intracranial and intraocular pressure—following head injury and glaucoma respectively.

Glycerol is effective orally. It reduces intraocular and intracranial pressure.

Methylxanthines like theophylline have mild diuretic effect.

Drug Interactions with Diuretics

1. Frusemide and ethacrynic acid are highly protein bound and may compete with drugs like warfarin and clofibrate for protein binding sites.
2. Other ototoxic drugs like aminoglycosides should not be used with loop diuretics to avoid enhanced toxicity.
3. Hypokalaemia induced by diuretics enhance digitalis toxicity.
4. NSAIDs blunt the effect of diuretics as they cause salt and water retention to avoid enhanced toxicity.
5. Diuretics enhance lithium toxicity by reducing renal excretion of lithium.
6. Other drugs that cause hyperkalaemia (ACE inhibitors) and oral K^+ supplements should be avoided with K^+ sparing diuretics because, given together they can cause severe hyperkalaemia.

DIURETICS AND DENTISTRY

1. When a patient is on concurrent medication with anticoagulants like warfarin and diuretics like frusemide profound anticoagulant activity would be present. Minor dental procedures including dental extraction can cause severe bleeding.
2. When a patient is already receiving frusemide or other loop diuretics, avoid using aminoglycoside antibiotics as the ototoxicity can get added up.
3. It is necessary to be cautious when it is required to give any of the NSAIDs to a patient who is already receiving diuretics

because NSAIDs blunt the diuretic effect. However one or two doses of analgesics does not matter much.

ANTI-DIURETICS

Antidiuretics are drugs that reduce urine volume. These include

1. Antidiuretic hormone (Vasopressin)
2. Thiazide diuretics
3. Miscellaneous
 - Chlorpropamide
 - Carbamazepine.

Antidiuretic hormone (ADH) is secreted by the anterior pituitary along with oxytocin. It is synthesized in the supraoptic and paraventricular nuclei of the hypothalamus, transported along the hypothalamo-hypophyseal tract to the posterior pituitary and is stored there.

ADH is released in response to two stimuli—dehydration and rise in plasma osmolarity.

Vasopressin Receptors

ADH acts on V_1 and V_2 receptors. V_1 receptors are present in vascular and other smooth muscles, kidneys and anterior pituitary while V_2 receptors are present in collecting duct in the kidneys. (See Fig 13.4).

Actions

ADH enhances water reabsorption by acting on the collecting duct. ADH activates the V_2 receptors present on the cell membrane of the collecting duct and increases the water permeability of these cells. ADH causes vasoconstriction and raises BP mediated by V_1 receptors. It also acts on other smooth muscles to increase peristalsis in the gut and contracts the uterus.

Vasopressin is given parenterally as injection- SC/IM/IV.

Adverse Effects

When used intranasally ADH can cause nasal irritation, allergy, rhinitis and atrophy of nasal mucosa. Other effects include nausea, abdominal cramps and backache (due to contractions of the uterus).

Uses

1. Diabetes insipidus of pituitary origin—Desmopressin is the preparation used. It should be used life long.
2. Bleeding oesophageal varices—ADH constricts mesenteric blood vessels (V_1 receptors) and may help. Analogs like desmopressin, terlipressin and lypressin can be used.
3. Before abdominal radiography—expels gases from the bowel.
4. Haemophilia and Von Willebrand's disease - ADH may release factor VIII and prevent bleeding.

Vasopressin Analogs

Desmopressin is selective for V_2 receptors and is longer acting. It is given as nasal spray. *Terlipressin* is longer acting while *felypressin* is short acting. *Felypressin* is used with local anaesthetics to prolong the duration of action because of its vasoconstrictor properties. *Lypressin* is another analog used in place of ADH.

Miscellaneous

Thiazides Paradoxically thiazides reduce urine volume in diabetes insipidus of both pituitary and renal origin by an unknown mechanism.

Chlorpropamide an oral hypoglycaemic, sensitizes the kidney to ADH action.

Carbamazepine an antiepileptic, stimulates ADH secretion.

14

Cardiac Glycosides and Treatment of Cardiac Failure

The cardiac muscle is a specialised tissue with unique properties like excitability, contractility and automaticity. The myocardium has two types of cells—the contracting cells and the conducting cells. The contracting cells participate in the pumping action of the heart. Parts of the conducting tissue have the characteristic property of automaticity. *Automaticity* is the ability of the cell to generate electrical impulses spontaneously. SA node, AV node and His-Purkinje system comprise the conducting tissue of the heart. Normally the SA node acts as the pace maker. *Excitability* is the ability of the cell to undergo depolarization in response to a stimulus. *Contractility* is the ability of the myocardium to adequately contract and pump the blood out of the heart. *Cardiac action potential* When a stimulus reaches the cardiac cell, specific ions move into and out of the cell eliciting an action potential. Such movement of ions across the cardiac cell may be divided into phases (Fig. 14.1).

Phase 0 is rapid depolarisation of the cell membrane during which there is fast entry of sodium ions into the cell through the sodium channels. This is followed by repolarisation.

Phase 1 is a short, initial, rapid repolarisation due to efflux of potassium ions.

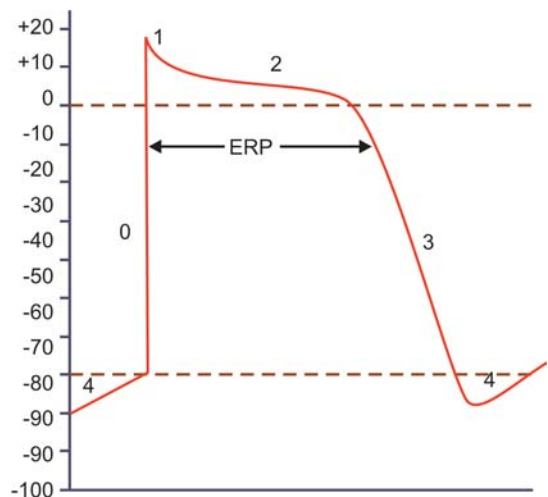


Fig. 14.1: Cardiac action potential phases 0-4: Phase 0—indicates rapid depolarisation, Phases 1-3—indicate repolarisation, Phase 4—gradual depolarisation during diastole

Phase 2 is a prolonged plateau phase due to slow entry of calcium ions into the cell through the calcium channels. Cardiac cell differs from other cells in having this phase of action potential.

Phase 3 is a second period of rapid repolarisation with potassium ions moving out of the cell.

Phase 4 is the resting phase during which potassium ions return into the cell while sodium and calcium ions move out of it and the resting membrane potential is restored.

During phases 1 and 2, the cell does not depolarise in response to another impulse, i.e. it is in absolute refractory period. But during phases 3 and 4, the cell is in relative refractory period and may depolarise in response to a powerful impulse.

The cardiac output is determined by heart rate and stroke volume. The stroke volume in turn depends on the preload, afterload and contractility. *Preload* is the load on the heart due to the volume of blood reaching the left ventricle. It depends on the venous return. *Afterload* is the resistance to the left ventricular ejection, i.e. the total peripheral resistance.

Congestive cardiac failure (CCF) is one of the common causes of morbidity and mortality. In congestive cardiac failure, the heart is unable to provide adequate blood supply to meet the body's oxygen demand. The pumping ability of the heart is reduced and the cardiac output decreases. The ventricles are not completely emptied resulting in increased venous pressure in the pulmonary and systemic circulation. This causes pulmonary oedema, dyspnoea, liver enlargement and peripheral oedema. As a compensatory mechanism, there is stimulation of the sympathetic system, renin angiotensin system and release of atrial natriuretic peptides which help in maintaining the cardiac output. Atria, ventricles and vascular endothelium store natriuretic peptides and release them in volume overload. These peptides increase renal excretion of salt and water and dilate vascular smooth muscles. The myocardium also undergoes structural alterations like ventricular hypertrophy and remodelling to adapt itself to the stressful situation. These compensatory changes maintain the cardiac output for sometime.

Depending on the cardiac output, cardiac failure may be of two types-low output failure and high output failure.

Low output failure could result from ischaemic heart disease, hypertension, valvular and congenital heart diseases. High output failure results from anaemia, thyrotoxicosis, beriberi and certain congenital heart diseases.

The drugs used in CCF include *diuretics*, *vasodilators* and *cardiac glycosides*. The pharmacology of cardiac glycosides has been discussed first, followed by the role of other drugs in CCF.

CARDIAC GLYCOSIDES

Cardiac glycosides are obtained from the plants of the foxglove family. Though these plants were known to Egyptians 3000 years ago, they were irrationally used. William Withering, an English physician first described the clinical effects of digitalis in CCF in 1785.

Source Digitoxin is obtained from the leaves of *Digitalis purpurea*. From the leaves of *Digitalis lanata*, digitoxin and digoxin are derived and the seeds of *Strophanthus gratus* contain ouabain. They are all called cardiac glycosides but digoxin is the most commonly used of them because of its favourable pharmacokinetic properties. The word digitalis is used to mean cardiac glycosides.

Chemistry The glycosides consist of an aglycon attached to sugars. The aglycon has pharmacodynamic activity while sugars influence pharmacokinetic properties.

Pharmacological Actions

1. Cardiac actions

- *Positive inotropic effect* Cardiac glycosides are cardiotonic drugs - they increase the force of contraction of the heart - the stroke volume increases and thereby the cardiac output. The systole is shortened and the diastole is prolonged which allows more rest to the heart. The ventricles are more completely emptied because of more forceful contractions.

- The *heart rate* is reduced due to:
 - a. increased vagal tone
 - b. decreased sympathetic overactivity due to improved circulation
 - c. by a direct action on SA and AV nodes.

The effects on *electrophysiological properties* of the heart varies with dose and in different parts of the heart. Digitalis shortens ventricular refractory period, depresses AV conduction and enhances automaticity of the ventricles and the Purkinje cells. Digitalis also produces the characteristic ECG changes.

- *Blood pressure* No significant effects in CCF patients. Pulse pressure may increase.
 - *Coronary circulation* improves due to increased cardiac output and prolonged diastole during which the coronaries get filled better.
2. *Extracardiac actions*
- *Kidney*—Diuresis occurs which relieves edema in CCF patients.
 - *CNS*—High doses stimulate CTZ resulting in nausea and vomiting.

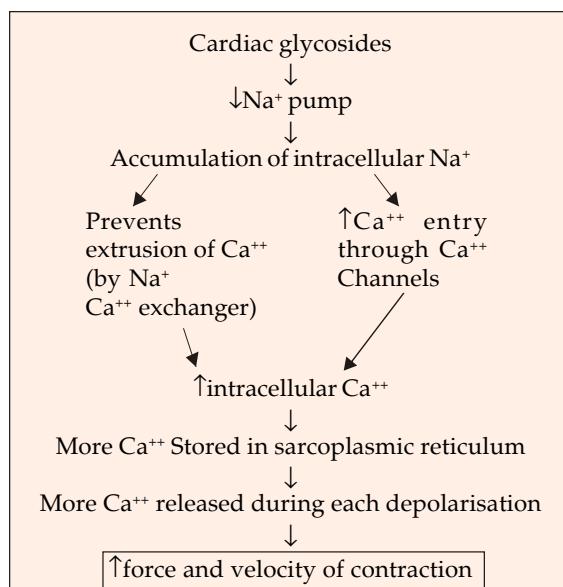


Fig. 14.2: Mechanism of action of cardiac glycosides

Mechanism of action Cardiac glycosides inhibit the enzyme Na^+K^+ ATPase—also called the ‘sodium pump’ present on the cardiac myocytes (Fig. 14.2 and Fig. 14.3). Inhibition of this pump results in an increase in the intracellular Na^+ and Ca^{++} . Thus more calcium is available for contraction, resulting in increased force and velocity of contraction. This happens as follows—

Inhibition of the ‘sodium pump’ increases intracellular sodium because sodium gets accumulated. This prevents Ca^{++} extrusion from the cardiac cell (through $\text{Na}^+-\text{Ca}^{++}$ exchanger) and also drives more calcium into the cell during depolarisation through voltage-sensitive calcium channels. This excess calcium gets stored in the sarcoplasmic reticulum. As a result more calcium is available for contraction and thus an increased amount of calcium is released during each action potential resulting in an increased force and velocity of contraction.

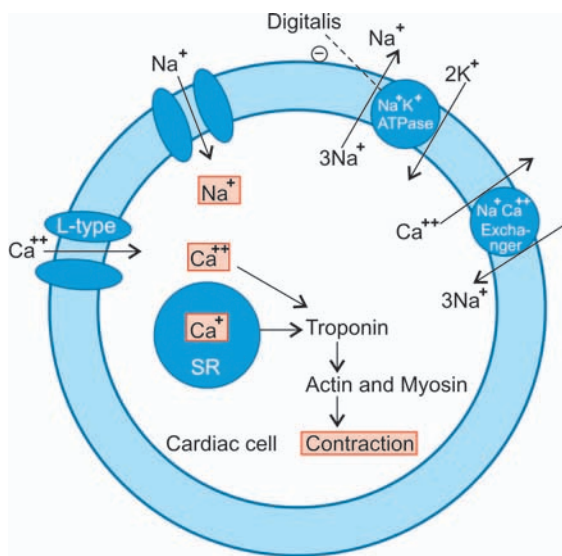


Fig. 14.3: Mechanism of action of cardiac glycosides. Cardiac glycosides inhibit the Na^+K^+ ATPase pump and ↑intracellular Na^+ which in turn prevents Ca^{++} extrusion. Thus more calcium is available for contraction. SR—Sarcoplasmic reticulum

Pharmacokinetics Digoxin is well-absorbed (Table 14.1). Presence of food in the stomach delays absorption. Bioavailability varies with different manufacturers and because the safety margin is low, in any given patient, the preparations from the same manufacturer should be used. Glycosides are cumulative drugs.

Digitalization Response to digitalis develops over 5-7 days with the maintenance dose as given in mild to moderate cases of CCF. But when rapid response is required, rapid digitalization can be done by more frequent dosing with constant monitoring.

Adverse effects Cardiac glycosides have a low safety margin and adverse effects are common. They inhibit Na^+/K^+ -ATPase in all excitable tissues - including neurons and smooth muscle cells where spontaneous activity is increased - responsible for toxicity.

Extracardiac Anorexia, nausea, vomiting and diarrhoea are the first symptoms to appear. Cardiac glycosides directly stimulate the CTZ. Weakness, confusion, hallucinations, blurred vision and gynaecomastia can occur. **Cardiac toxicity** Arrhythmias of any type including extrasystoles, bradycardia, pulses bigeminy and AV block (ventricular tachycardia and fibrillation) can be caused by cardiac glycosides. Hypokalaemia enhances digitalis toxicity (Table 14.2).

Treatment of Toxicity

- Stop digitalis
- Oral or parenteral K^+ supplements are given
- Ventricular arrhythmias are treated with IV lignocaine
- Bradycardia is treated with atropine and supraventricular arrhythmias with propranolol

Table 14.1: Compare and contrast digoxin and digitoxin

Properties	Digoxin	Digitoxin
1. Source	<i>Digitalis lanata</i>	<i>Digitalis purpurea and lanata</i>
2. Pharmacokinetics		
• Route of administration	Oral, IV	Oral
• Absorption	40-60%	90-100%
• Plasma protein binding	25%	95%
• Onset of action	15-30 min	30-120 min
• $t_{1/2}$	24-48 hr	5-7 days
• Time for digitalization (without loading dose)	5-7 days	25-30 days
3. Dose		
• Daily dose (slow loading or maintenance)	0.125-0.5 mg	0.05-0.2 mg
• Rapid digitalising dose	0.5-0.75 mg every 8 hours 3 doses	0.2-0.4 mg every 12 hours 3 doses
• Route of elimination	Renal excretion	Hepatic metabolism
4. Used for	• Most used among cardiac glycosides • Used for initiation and maintenance therapy	• Less often used • Used only for maintenance therapy

- In severe toxicity—antidigoxin immunotherapy (antidigoxin antibodies) is now available. It can be life saving in severe digoxin overdosage.

Uses

1. Congestive cardiac failure (see below)
2. Cardiac arrhythmias
 - Atrial fibrillation and atrial flutter—digoxin reduces the ventricular rate
 - Paroxysmal supraventricular tachycardia (PSVT)—digoxin is an alternative to verapamil.

Precautions and contraindications to digitalis therapy

- Hypokalaemia—enhances toxicity
- MI, thyrotoxicosis patients and elderly—more prone to arrhythmias
- Acid base imbalance—prone to toxicity.

Other Positive-inotropic Drugs

Phosphodiesterase inhibitors—Amrinone (inamrinone) and milrinone—These drugs inhibit the enzyme phosphodiesterase (which degrades cAMP) resulting in ↑cAMP levels. They increase the force of contraction and also cause vasodilatation. But because of the adverse effects and increased mortality seen with the use of these drugs, they are generally not preferred. However, they may be used for short periods in severe heart failure. Milrinone has shorter $t_{1/2}$ and fewer side effects.

Table 14.2: Drug interactions

<i>Drugs that enhance digoxin toxicity</i>	
•	Diuretics (due to hypokalaemia), calcium
•	Quinidine, verapamil, methyldopa—↑digoxin levels
<i>Drugs that reduce digoxin levels</i>	
•	Antacids, neomycin, metoclopramide—↓ absorption
•	Rifampicin, phenobarbitone—hasten metabolism due to enzyme induction

DRUGS USED IN CONGESTIVE CARDIAC FAILURE

In congestive cardiac failure, the heart is unable to provide adequate blood supply to meet the demand. The aim of treatment is to reduce morbidity and mortality by restoring cardiac output and relieving congestion.

The drugs used in CCF include:

1. Diuretics
 2. Vasodilators
 3. Positive inotropic agents -
 - Digitalis
 - β adrenergic agonists
 - Phosphodiesterase (PDE) inhibitors
 - Others
1. **Diuretics** High ceiling diuretics like frusemide are used. They increase salt and water excretion and reduce blood volume. By this they reduce preload and venous pressure, improve cardiac performance and relieve oedema.
 2. **Vasodilators** reduce the mortality in patients with cardiac failure. Vasodilators may be arteriolar or venular dilators or both.
 - Arteriolar dilators (↓ after load) — hydralazine-relax arterial smooth muscles, thus reducing peripheral vascular resistance (↓ afterload). As a result, the work load on the heart is reduced.
 - Venodilators (↓ preload) — nitrates - reduce the venous return to the heart (↓ preload) thus reducing the stretching of the ventricular walls and myocardial oxygen requirements.
- Organic nitrates:** Nitroglycerine and isosorbide dinitrate are good vasodilators with a rapid and short action. They can be used for short periods to decrease the ventricular filling pressure in acute heart failure. Nitroglycerine can be used IV in acute CCF. Nitrates may be given in combination with hydralazine.

- Both arteriolar and venular dilators—ACE inhibitors, sodium nitroprusside, prazosin, calcium channel blockers - these reduce both preload and afterload.

Angiotensin converting enzyme inhibitors (ACE-I) (Page 111) like captopril, enalapril, lisinopril and ramipril act by -

- reduction of afterload* Angiotensin II is a powerful vasoconstrictor present in the plasma in high concentrations in cardiac failure. ACE-I prevent the conversion of angiotensin I to angiotensin II and thereby reduce the after load.
- reduction of preload* Aldosterone causes salt and water retention and increases plasma volume. ACE-I prevent the formation of aldosterone (by reducing Ang-II) and thereby reduce the preload. They also prevent bradykinin degradation and increase bradykinin levels which also causes vasodilatation.
- reversing compensatory changes* Angiotensin II formed locally in the myocardium is responsible for various undesirable compensatory changes like ventricular hypertrophy and ventricular remodelling seen in CCF. ACE-I reverse these changes.

ACE inhibitors are the most preferred drugs in chronic congestive cardiac failure.

Sodium nitroprusside is a powerful vasodilator. Since it dilates both arterioles and venules, it reduces both ventricular filling pressure and peripheral arterial resistance. It is given IV, has a rapid (30-60 sec) and short action (3 minutes). Hence it is useful in acute severe heart failure.

Prazosin an α_1 antagonist, is a vasodilator. It can be used in acute heart failure for longer periods than nitrates.

Calcium channel blockers are not routinely used. Amlodipine or felodipine may be tried in

patients in whom other vasodilators are contraindicated.

3. Positive inotropic agents

Digitalis: Mild to moderate cases of low output failure are treated with diuretics and vasodilators (ACE-inhibitors preferred). When patients are not controlled by these, they may be given digoxin. Digoxin improves cardiac performance in the dilated, failing heart. If there is associated atrial fibrillation, digoxin is the preferred drug in such patients.

β adrenergic agonists: Dobutamine is a positive inotropic agent. It stimulates the cardiac β_1 receptors and enhances the force of contraction of the cardiac muscle. It increases the cardiac output without significant tachycardia. It also produces some vasodilation by stimulating the β_2 receptors. Dopamine may be used in patients with associated renal impairment because dopamine increases renal perfusion in addition to increased cardiac output.

PDE Inhibitors: Amrinone or milrinone may be used for short periods to enhance the cardiac output in severe heart failure.

4. Others

β Adrenergic blockers : Though β blockers are negative inotropic agents, several recent studies have shown that when used carefully along with other drugs, β blockers can improve long-term survival (Page 80).

Cardiac Failure and Dentistry

1. The antibiotic neomycin can reduce digoxin absorption and could worsen CCF. Alternative antibiotic may be used if its long-term use is required.
2. Use of NSAIDs especially long-term use can cause salt and water retention and worsen CCF.
3. A knowledge of CCF is necessary as a dentist has to be careful while carrying on surgical procedures in such patients.

15

Calcium Channel Blockers

The discovery of the calcium channels in the cardiac cells helped in understanding the mechanisms involved in smooth muscle contraction. Verapamil was the first agent found to have calcium channel blocking properties and now we have many more.

Dihydropyridines

Nifedipine	Nicardipine
Nimodipine	Nitrendipine
Nisoldipine	Felodipine
Amlodipine	Isradipine

Others

Verapamil	Diltiazem
	Bepridil

The depolarisation of the cardiac and vascular smooth muscle cells depend on the entry of extracellular calcium into the cell through the calcium channels. Intracellular calcium is also increased by receptor-mediated action – i.e. agonist induced calcium release. This calcium triggers the release of intracellular calcium from the sarcoplasmic reticulum. All these calcium ions bring about contraction of the cardiac and vascular smooth muscle cells.

Calcium channel antagonists inhibit the entry of calcium by blocking the L-type of calcium channels. (There are 3 types of

calcium channels - L, N and T types). This decreases calcium current and calcium entry into cardiac and vascular smooth muscle cells resulting in the following effects—

1. *Vascular smooth muscle* Relaxation of the arteriolar smooth muscles results in reduced peripheral vascular resistance and blood pressure. The effect on venous beds is not significant. Reflex tachycardia may occur with some CCBs like nifedipine. Dihydropyridine CCBs have prominent effects on the blood vessels, i.e. they are vascular selective.
2. *Heart* CCBs depress myocardial contractility, reduce heart rate and in higher doses they slow AV conduction. They reduce cardiac work and thereby myocardial oxygen consumption. Verapamil, bepridil and diltiazem have prominent cardiac effects.
3. *Coronary circulation* CCBs dilate the coronary vessels, increasing the coronary blood flow. Hence they are useful in variant angina.
4. *Other effects*
 - Nimodipine is highly lipid soluble, crosses the BBB and relaxes the cerebral blood vessels.
 - CCBs relax the uterus and may be useful in premature labour.

Pharmacokinetics CCBs are well-absorbed but undergo extensive first pass metabolism. They are all highly plasma protein bound and are metabolized in the liver.

Verapamil has prominent myocardial depressant actions. AV conduction is depressed and usually bradycardia is seen. Hence it should not be combined with β -blockers. Fall in BP is mild as the vasodilator effect of verapamil is less potent. **Diltiazem** has less potent vasodilator effects but is a myocardial depressant.

Adverse effects of verapamil and diltiazem include constipation, bradycardia, heart block, hypotension and skin rashes. They may precipitate CCF in patients with diseased heart.

Dihydropyridine CCBs

Nifedipine is a potent vasodilator and causes a significant fall in BP and evokes reflex tachycardia. Myocardial depressant effect is weak (table 15.1). It can be given sublingually.

Adverse effects of nifedipine are headache, flushing, palpitation, dizziness, fatigue, hypotension, leg cramps and ankle oedema. Long term use can cause gum hypertrophy.

Other Dihydropyridines Like

- Amlodipine, felodipine, nitrendipine and nifedipine are similar to nifedipine with

some pharmacokinetic variations. They have higher vascular selectivity.

- Amlodipine, felodipine, nitrendipine and nisoldipine are longer acting and can be given once daily.
- Nimodipine selectively relaxes cerebral vasculature as it crosses the BBB because it is highly lipid soluble.

Therapeutic Uses of CCBs

1. Angina pectoris – CCBs are useful in the prophylaxis of patients with exertional angina as they decrease myocardial oxygen demand and bring about coronary vasodilatation. CCBs are also useful in variant angina as they bring about coronary vasodilation.
2. Hypertension – Long acting CCBs or sustained release preparations may be used in chronic hypertension. In hypertensive crisis nifedipine is used sublingually or the capsule is bitten and swallowed.
3. Arrhythmias – Verapamil, diltiazem and bepridil have antiarrhythmic properties. Verapamil is used in PSVT and to control ventricular rate in atrial flutter or fibrillation.
4. Peripheral vascular disease – Nifedipine, felodipine and diltiazem can be used in Raynaud's disease for their vasodilator effects.

Table 15.1: Compare and contrast verapamil and nifedipine

	<i>Verapamil</i>	<i>Nifedipine</i>
1. Bioavailability	Poor (20-35%)	Good (50-70%)
2. Sublingual form	Not available	Available
3. $t_{1/2}$	6 hrs	4 hrs
4. Effects on heart	Prominent	Weak
5. Effects on vasculature	Mild	Prominent
6. Reflex tachycardia	Negligible	Prominent
7. Use in arrhythmias	Used	Not used

5. Other uses

- (i) Hypertrophic cardiomyopathy - Verapamil can be beneficial due to its negative inotropic effects on the heart.
- (ii) Migraine – Verapamil is useful in the prophylaxis of migraine
- (iii) Subarachnoid haemorrhage – Vasospasm that follows subarachnoid haemorrhage is believed to be responsible for neurological defects. As nimodipine brings about cerebral vasodilatation, it is used to treat neurological deficits in patients with cerebral vasospasm.

- (iv) Preterm labour – Nifedipine inhibits uterine contractions and is found to be useful in delaying labour in premature uterine contractions.

Drug Interactions

- Verapamil and diltiazem should be avoided in patients receiving beta-adrenergic blockers because the myocardiac depressant effects get added up.
- Verapamil can precipitate digoxin toxicity by increasing digoxin levels (verapamil reduces digoxin excretion).

16

Antiarrhythmic Drugs

Arrhythmia is an abnormality of the rate, rhythm or site of origin of the cardiac impulse or an abnormality in the impulse conduction. The word dysrhythmia is also used by some. Cardiac arrhythmias may be due to abnormal generation or conduction of impulses. Factors like myocardial hypoxia, myocardial ischaemia, electrolyte disturbances, trauma, drugs and autonomic influences can cause arrhythmias.

Arrhythmias may be tachyarrhythmias, bradyarrhythmias or digitalis-induced arrhythmias. Based on the site of impulse origin, they may be grouped as supra-ventricular (SA node, AV node, atria) or ventricular arrhythmias (in ventricles). Ventricular arrhythmias are a common cause of death, particularly sudden death.

CLASSIFICATION

Based on the cardiac cycle, Vaughan Williams classified antiarrhythmics as follows:

Class I. Sodium channel blockers

- A. Prolong repolarization
 - Quinidine, procainamide, disopyramide, moricizine
- B. Shorten repolarization
 - Lignocaine, mexiletine, phenytoin
- C. Little effect on repolarization
 - Encainide, flecainide, propafenone

Class II. β -adrenergic blockers

(reduce sympathetic tone)
- Propranolol, acebutolol, esmolol, etc.

Class III. K^+ channel blockers

(Prolong repolarization)
- Amiodarone, bretylium, sotalol, dofetilide, ibutilide

Class IV. Ca^{++} channel blockers

(Prolong conduction and refractoriness specially in SA and AV nodes)
- Verapamil, diltiazem

Sodium Channel Blockers

Mechanism of action All drugs in Class I block the sodium channels and prevent the inward movement of Na^+ ions. The sodium channels exist in three states—resting, open and inactivated (refractory) state. Sodium channel blockers preferentially bind Na^+ channels in the open and inactivated state and thus interfere with depolarisation.

Class IA drugs block Na^+ channels and depress phase-0 depolarisation. They also prolong repolarisation by blocking K^+ channels. (Fig. 16.1)

Quinidine

Quinidine is the D-isomer of quinine obtained from the cinchona bark. By blocking Na^+ channels, it depresses all cardiac

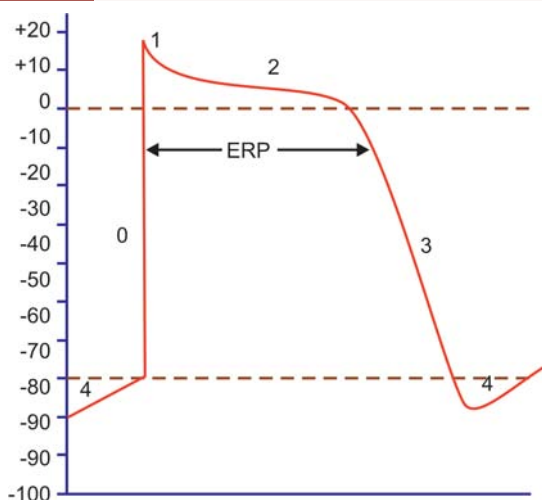


Fig. 16.1: Cardiac action potential: Phase 0-rapid depolarisation, phase 1-initial rapid repolarisation, phase 2-prolonged plateau phase, phase 3-second rapid repolarisation, phase 4-resting phase

properties—automaticity, excitability, conduction velocity and prolongs repolarization - quinidine thus has membrane-stabilizing activity, i.e. it inhibits the propagation of the action potential.

Quinidine also has vagolytic and α -blocking properties. It is also a skeletal muscle relaxant.

Pharmacokinetics Given orally quinidine is rapidly absorbed, 90% bound to plasma proteins, metabolised in the liver and excreted in the urine.

Adverse effects Quinidine is not well-tolerated due to adverse effects and may need to be stopped.

Cardiac Quinidine itself can cause arrhythmias and heart block. It can also cause hypotension, prolongation of QT interval and *torsades de pointes*. *Torsades de pointes* refers to polymorphic ventricular tachycardia and is so called because of the pattern of EEG changes - in French, it means twisting of points. All drugs which prolong QT interval can also cause this. Hence treatment should be monitored.

Non-cardiac - Diarrhoea, nausea, vomiting and hypersensitivity reactions including thrombocytopenia and rarely bone marrow depression, hepatitis and idiosyncratic reactions can occur. Higher doses can cause cinchonism like quinine.

Drug Interactions

- Quinidine is a microsomal enzyme inhibitor. It raises the plasma levels of propafenone and reduces the conversion of codeine to morphine thereby decreasing its analgesic efficacy.
- Microsomal enzyme inducers like phenytoin and phenobarbitone enhance metabolism of quinidine resulting in therapeutic failure.
- Quinidine reduces the clearance of digoxin thereby precipitating digoxin toxicity.

Procainamide a derivative of the local anaesthetic procaine has the advantages over quinidine that it has weak vagolytic properties and is not an α -blocker. It is better tolerated than quinidine and can cause nausea, vomiting and hypersensitivity reactions including lupus syndrome. Higher doses can cause hypotension, heart block and *torsades de pointes*.

Disopyramide has significant anticholinergic properties which is responsible for adverse effects like dry mouth, blurred vision, constipation and urinary retention. It can also cause *torsades de pointes*.

Uses Class IA drugs are useful in almost all types of arrhythmias (Table 16.1). They are used in atrial fibrillation and atrial flutter for maintenance of sinus rhythm and in ventricular arrhythmias to prevent recurrence. Because of the adverse effects, quinidine and procainamide are not preferred by most practitioners in arrhythmias but quinidine can be used in malaria in place of quinine.

Class IB Drugs

Class IB drugs block the sodium channels and also shorten repolarization.

Lignocaine suppresses the electrical activity of the arrhythmogenic tissues while the normal tissues are not much affected. It is a local anaesthetic. Given orally lignocaine undergoes high first pass metabolism and has a short $t_{1/2}$ —hence used parenterally. It may cause drowsiness, hypotension, blurred vision, confusion and convulsions. Lignocaine is used in the treatment of

ventricular arrhythmias, especially that caused by acute myocardial infarction or open heart surgery. Lignocaine is not useful in atrial arrhythmias and the reason for this is not clear. It could be because the atrial action potentials are so short that the sodium channels are in an inactivated state for a very short period and lignocaine is unable to block them.

Phenytoin is an antiepileptic also useful in ventricular arrhythmias (not preferred due to toxicity) and digitalis induced arrhythmias.

Table 16.1: Major causes and choice of drugs in cardiac arrhythmias

Arrhythmia	Cause	Treatment
<i>Sinus tachycardia</i>	↑ sympathetic tone, fever, thyrotoxicosis	• Treat the cause • If severe →propranolol
<i>Atrial extrasystoles</i>	Excess caffeine, nicotine, alcohol	• Treat the cause • Reassurance • If severe→propranolol / disopyramide
<i>Atrial flutter/fibrillation</i>	Rheumatic heart disease, cardiomyopathy, hypertension	• Cardioversion • Propranolol / quinidine/ disopyramide / digitalis
<i>PSVT</i>		• Vagal manouvers like carotid massage • Verapamil/adenosine • β-blockers
<i>Ventricular ectopics</i>	Normal heart—benign; also in cardiomyopathy, ischaemia, digitalis induced	• β-blockers • Lignocaine
<i>Ventricular tachycardia</i>	Organic heart disease, ventricular dysfunction, drug-induced	• Cardioversion • Lignocaine
<i>Ventricular fibrillation</i>	Acute MI, organic heart disease, surgical trauma, drug-induced	• Cardioversion • Lignocaine • Class I A drugs for prevention
<i>Digitalis induced tachyarrhythmias</i>	Digitalis toxicity	• Lignocaine • Potassium • Phenytoin
<i>Sinus bradycardia</i>		• Atropine

Mexiletine can be used orally; causes dose related neurologic adverse effects including tremors and blurred vision. Nausea is common. It is used as an alternative to lignocaine in ventricular arrhythmias.

Class IC Drugs

Class IC drugs are the most potent sodium channel blockers. Because of the risk of cardiac arrest, sudden death and other adverse effects, they are not commonly used. They may be used in severe ventricular arrhythmias and to maintain sinus rhythm in atrial fibrillation.

Class II Drugs

β -blockers (Chapter 12) like propranolol exert antiarrhythmic effect due to blockade of cardiac β receptors. They depress myocardial contractility, automaticity and conduction velocity. In higher doses they also have membrane stabilising activity like class I drugs.

Propranolol and cardioselective β blockers like atenolol and metoprolol are used in the treatment and prevention of supraventricular arrhythmias especially those associated with exercise, emotion or hyperthyroidism.

Esmolol given intravenously is rapid and short-acting and can be used to treat arrhythmias during surgeries, following myocardial infarction and other emergencies.

Class III Drugs

These drugs prolong the action potential duration and refractory period by blocking the potassium channels.

Amiodarone an analog of thyroid hormone is a powerful antiarrhythmic. It acts by multiple mechanisms.

- prolongs APD by blocking K^+ channels.
- blocks sodium channels.
- blocks β adrenergic receptors.

Amiodarone can cause various adverse effects like heart block, cardiac failure, hypotension, bluish discolouration of the skin, hypothyroidism, gastrointestinal disturbances and hepatotoxicity. It can cause pulmonary fibrosis that can be fatal.

Amiodarone is used only in resistant cases of chronic ventricular arrhythmias and to prevent recurrence of atrial fibrillation and flutter.

Bretylium is an adrenergic neurone blocker used in resistant ventricular arrhythmias.

Sotalol a β -blocker also prolongs the action potential duration and is classified under class III antiarrhythmic drugs and is often preferred when a β -blocker is needed.

Class IV Drugs

Calcium channel blockers (Page 96) inhibit the inward movement of calcium resulting in reduced contractility, automaticity and AV nodal conduction. Verapamil, diltiazem, and bepridil have prominent cardiac effects, because they block the calcium channels in the cardiac cells in therapeutic doses.

Verapamil is used to terminate paroxysmal supraventricular tachycardia (PSVT). It is also used to control ventricular rate in atrial flutter or fibrillation because it depresses the AV nodal conduction. Diltiazam can be used in place of verapamil.

Dofetilide is a newly introduced and selective K^+ channel blocker. It has no other actions as it is a pure K^+ channel blocker and prolongs APD. It is used orally in atrial fibrillation to convert and to maintain sinus rhythm. The only adverse effect known is *torsades de pointes* in 1% patients.

Ibutilide is a K^+ channel blocker used as intravenous infusion to quickly convert atrial flutter/fibrillation to sinus rhythm. It can cause *torsades de pointes*.

Drug Interactions

Verapamil displaces digoxin from tissue binding sites and also reduces its renal clearance resulting in digoxin toxicity - dose of digoxin should be reduced.

Other Antiarrhythmics

Adenosine, atropine, digoxin and magnesium sulphate also have antiarrhythmic properties but are not included in Vaughan Willams classification.

Adenosine is a purine nucleotide having rapid and short antiarrhythmic action. Given IV it suppresses automaticity, AV conduction and dilates the coronaries. Adenosine is the *drug*

of choice for acute termination of paroxysmal supraventricular tachycardias (PSVT).

Adverse effects are nausea, dyspnoea, flushing, dizziness and headache but are of short duration. Theophylline blocks adenosine receptors and inhibits the action of adenosine.

Atropine is used in sinus bradycardia. It acts by blocking M_2 muscarinic receptors.

Digitalis depresses AV conduction, reduces heart rate and increases the force of contraction of the myocardium. Digoxin is used in atrial fibrillation to control the ventricular rate.

Magnesium sulphate is used IV to treat digitalis induced arrhythmias and *torsades de pointes*.

17

Drugs Used in Angina Pectoris and Myocardial Infarction

Angina pectoris is the chief symptom of ischaemic heart disease (IHD) characterised by sudden, severe, substernal discomfort or pain which may radiate to the left shoulder and along the flexor surface of the left arm. Myocardial oxygen consumption depends on preload (determined by venous return and stretching of the heart), afterload (determined by peripheral arterial resistance) and heart rate. When the oxygen supply to the myocardium is insufficient for its needs, myocardial ischaemia develops. Pain is due to accumulation of metabolites in the cardiac muscle.

Two Forms of Angina are

1. *Classical angina (stable angina, angina of effort, exertional angina)* Pain is induced by exercise or emotion, both of which increase myocardial oxygen demand. In such patients there is narrowing of the coronary arteries due to atherosclerosis and therefore the coronaries cannot dilate to increase the blood supply during exercise. Hence there is an imbalance between oxygen supply and demand.
2. *Variant or Prinzmetal's angina* occurs at rest and is caused by spasm of the coronary artery.

Drugs are used to improve the balance between oxygen supply and demand either by increasing oxygen supply to the

myocardium (coronary dilation) or by reducing the oxygen demand (reducing preload/afterload/heart rate or all of these). Drugs used in the treatment of angina are as follows:

Classification

1. *Nitrates*
Nitroglycerine, isosorbide dinitrate, isosorbide mononitrate, penta erythritol tetranitrate.
2. *Calcium channel blockers*
Verapamil, diltiazem, amlodipine, nifedipine.
3. *β -blockers*
Propranolol, atenolol, etc.
4. *Potassium channel openers*
Nicorandil
5. *Miscellaneous*
Dipyridamole, aspirin, trimetazidine

Nitrates

Mechanism of action Nitrates are vasodilators (Fig. 17.1). They are converted to nitric oxide which activates vascular guanylyl cyclase which in turn increases the synthesis of cGMP. This cGMP catalyses the phosphorylation of protein kinases causing relaxation of the smooth muscles.

Pharmacological actions Nitrates are predominantly venodilators. Venodilation reduces venous return to the heart thereby

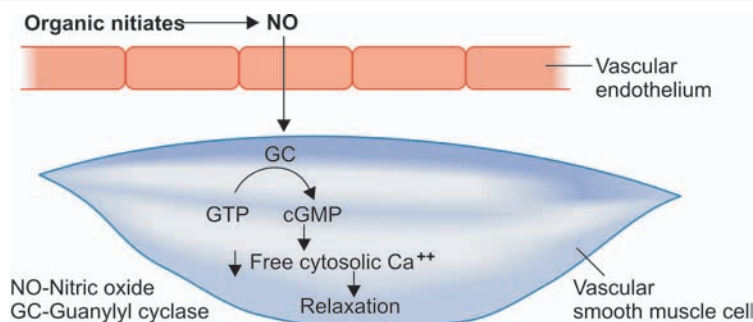


Fig. 17.1: Mechanism of action of nitrates

reducing preload. Arteriolar dilation reduces vascular resistance thus decreasing afterload. As both preload and afterload are reduced, workload of the heart is decreased thereby reducing oxygen requirement of the heart.

In variant angina, nitrates relieve vasospasm due to coronary vasodilation. Nitrates also cause dilation of blood vessels in the skin—resulting in flushing; dilatation of the meningeal vessels results in headache. Bronchial smooth muscles are also relaxed. *Pharmacokinetics* Nitrates are well absorbed orally but they undergo extensive first pass metabolism. Nitroglycerine, isosorbide dinitrate, (Table 17.1) isosorbide mononitrate and pentaerythritol tetranitrate are the nitrates used in angina. Amyl nitrate is used in cyanide poisoning.

Nitrates are available for oral, sublingual, parenteral use and as ointment and transdermal patches for topical use. Topical preparations are used for the prevention of nocturnal episodes of angina. But there is an increased risk of development of tolerance with topical and slow release preparations. *Adverse effects* Headache is common; flushing, sweating, palpitation, weakness, postural hypotension and rashes can occur. Tolerance to vascular effects of nitrates develops on repeated long term use particularly when

continuous high plasma nitrate levels are present. By adopting proper dosing schedule, tolerance can be avoided. The patient must be free of nitrates for at least 8 hours of the day to prevent the development of tolerance. Tolerance can also be minimized by twice/thrice daily dosing schedule.

Uses

1. *Angina* Sublingual nitroglycerine is the drug of choice for acute anginal attacks. It relieves pain in 3 minutes. If the pain is not relieved, the dose may be repeated (up to 3 tablets in 15 minutes). Nitrates are also used orally for the prophylaxis of angina. Longer acting nitrates are preferred for this. Nitroglycerine ointment may be applied over the chest.
2. *Cardiac failure* Nitrates are useful due to their vasodilator property (see page 95).
3. *Myocardial infarction* IV nitroglycerine is used by many physicians to reduce cardiac work.
4. *Cyanide poisoning* Cyanide rapidly binds to cytochrome oxidase and other vital enzymes resulting in inhibition of cellular respiration and blocks the utilization of oxygen. It requires immediate treatment.

Table 17.1: Some nitrates used in angina pectoris

Drug	Dose and route	Duration of action
Nitroglycerine (GTN) (ANGISED)	0.5 mg SL	15-40 min
	5 mg oral	4-8 hr
	2% Skin ointment applied 1-2 inches on the precordial region	4-6 hr
Isosorbide dinitrate (SORBITRATE)	5-10 mg SL	20-40 min
	10-20 mg oral	2-3 hr
Isosorbide mononitrate (ISMO)	10-20 mg oral	6-8 hr

Amylnitrite is given by inhalation and sodium nitrite by IV injection (10 ml of 3% solution). Sodium thiosulphate is given IV (50ml of 25% solution). It reacts with cyanmethaemoglobin to form thiocyanate which is easily excreted by the kidneys. Nitrates convert haemoglobin to methaemoglobin which has a high affinity for cyanide and binds to cyanide forming cyanmethaemoglobin. It thus protects the important enzymes from binding to cyanide. Amyl nitrite is preferred. Early treatment is very important.

Calcium Channel Blockers (Chapter 15)

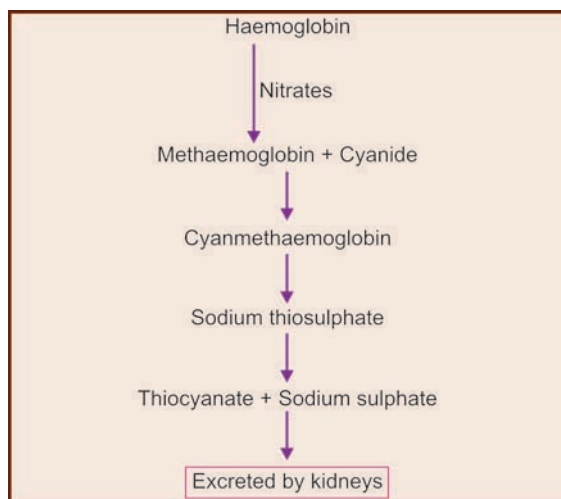
CCBs relax the arterioles leading to a decrease in the peripheral vascular resistance and a reduction in the afterload. Some reflex

tachycardia can occur particularly with dihydropyridines. But CCBs also depress the myocardial contractility thereby reducing the heart rate and force of contraction. This results in reduced cardiac workload and oxygen consumption. CCBs also dilate the coronaries thereby increasing the coronary blood flow.

CCBs are used for the prophylaxis of exertional angina. They can be combined (except verapamil) with beta blockers like propranolol. CCBs are also useful in vasospastic angina since they dilate the coronaries and relieve vasospasm. Infact they are preferred over nitrates in vasospastic angina.

β -blockers

β -blockers reduce the frequency and severity of attacks of exertional angina and are useful in the prevention of angina. Exercise, emotion and similar situations increase sympathetic activity leading to increased heart rate, force of contraction and BP, thereby increasing O_2 consumption by the heart. β -blockers prevent angina by blocking all these actions (Chap. 12). They are used for the long-term prophylaxis of classical angina and may be combined with nitrates. β -blockers should always be tapered after prolonged use. They are *not* useful in variant angina.



Potassium Channel Openers

Nicorandil is an arterial and venous dilator. Opening of the ATP-sensitive K^+ channels results in efflux of K^+ leading to hyperpolarization and therefore relaxation of the vascular smooth muscles. In addition it also acts through NO like nitrates. It is tried in angina when other drugs do not afford significant benefit. It is expensive. Dose 10-20mg twice daily.

Adverse effects are headache, flushing, palpitation, dizziness and hypotension.

Pinacidil is similar to nicorandil. It is useful in angina and hypertension.

Miscellaneous

Dipyridamole is a coronary vasodilator but it diverts the blood from ischaemic zone and is therefore not beneficial. It inhibits platelet aggregation for which it is used in post MI and post-stroke patients for prevention of coronary and cerebral thrombosis.

Aspirin Long-term administration of low dose aspirin is recommended to prevent myocardial infarction.

Trimetazidine is a calcium channel blocker claimed to have a protective effect on the ischaemic myocardium and to maintain left ventricular function. It is tried in exertional angina - 20 mg t.d.s.

Pharmacotherapy of Angina

Exertional Angina

Acute attack Sublingual nitroglycerine 0.5 mg is the drug of choice. If the pain does not subside in 5 minutes, repeat the dose. After the relief of pain, the tablet should be discarded. If the pain does not subside with 3 tablets, physician should be consulted as the pain may be of myocardial infarction.

Acute prophylaxis Sublingual nitroglycerine given 15 minutes before an exertion (e.g. walking uphill) can prevent the attack. The prophylactic effect lasts for 30 minutes.

Chronic prophylaxis Long-acting nitrates or β -blockers (preferred) or calcium channel blockers can be used. All are given orally.

If one drug is not effective, a combination of drugs may be used.

Vasospastic Angina

Nitroglycerine and nifedipine given sublingually are effective in preventing and treating vasospastic episodes.

Combinations of Drugs in Angina

1. Nitrates + β -blockers—Very effective in exertional angina. Reflex tachycardia due to nitrates is countered by β -blockers. Ventricular dilatation due to β -blockers is opposed by nitrates.
2. Nifedipine + β -blockers—The antianginal effects are additive. Reflex tachycardia due to nifedipine is countered by β -blockers.
3. Nitrates + CCBs—Nitrates decrease preload, CCBs reduce afterload and the combination reduces cardiac workload.
4. CCBs + β -blockers + Nitrates—If the angina is not controlled by 2 drug combinations, 3 drugs can be used. Nitrates reduce preload, CCBs reduce afterload while β -blockers decrease heart rate. This combination is useful in severe angina.

UNSTABLE ANGINA

Unstable angina includes:

- patients with exertional angina developing angina at rest
- severe, prolonged anginal attacks without ECG evidence of MI
- angina developing after myocardial infarction.

Such patients with unstable angina are at a high risk of developing MI or sudden death and need hospitalisation and rigorous treatment for its prevention.

Drugs used in unstable angina are-

1. Aspirin – Platelet aggregation can occlude narrowed coronary arteries and can also release potent vasoconstrictors. Aspirin (75-300 mg daily) prevents platelet aggregation and thereby could prevent myocardial infarction.
2. Heparin–In high risk patients IV/SC heparin reduces pain.
3. Nitrates–Intravenous nitroglycerine relieves pain.
4. Other drugs– β adrenergic blockers like atenolol (50-100 mg daily) may be given; if they are to be avoided for some reason, calcium channel blockers like verapamil may be given. Glycoprotein receptor antagonists (abciximab, integrilin and tirofiban) inhibit the final steps of platelet aggregation and are being tried in unstable angina.

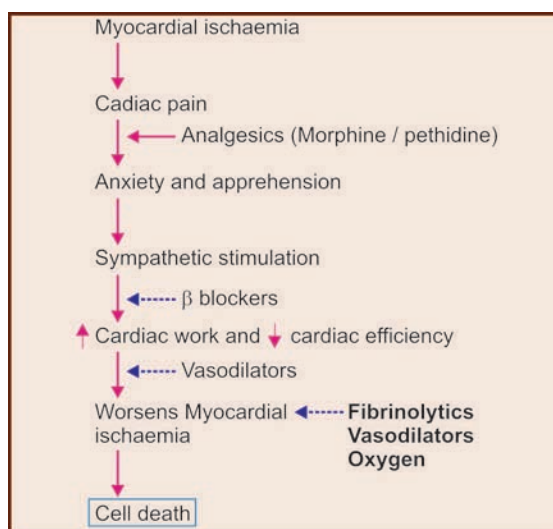
DRUGS USED IN MYOCARDIAL INFARCTION

Coronary heart disease is the most important cause of premature death, particularly in the developed countries.

Rupture of an atheromatous plaque in the coronary artery results in an occlusive thrombus leading to acute myocardial infarction. The process of infarction gradually develops (unless it is severe) over 6-8 hours after which there is cell death in the infarcted area. But timely intervention can reduce the extent of damage. The immediate objective of treatment is to limit the myocardial ischemia and the consequent cell death.

Immediate Treatment

1. *Analgesia* - Morphine 10 mg or pethidine 50 mg is given intravenously through an IV cannula. They relieve pain and thereby reduce anxiety. Hence the demerits of sympathetic overactivity are reduced. Diazepam may also be given to reduce anxiety and produce sedation.



2. *Thrombolytics* – Streptokinase 1.5 million units infusion is given over 1 hour. Alternatively alteplase or other thrombolytics may be given. Thrombolytics should be *started at the earliest possible* (within 6 - 12 hours) as they can limit the extent of damage and reduce mortality.
3. *Aspirin* – 300 mg of soluble aspirin given orally reduces mortality and improves the effect of thrombolysis. It should be continued (75-150 mg/day) even after the patient recovers.
4. *Oxygen* – High flow oxygen should be given by inhalation.
5. *Other drugs*
 - (i) β – *adrenergic antagonists*– IV atenolol (5–10 mg over 5 minutes) reduces short-term mortality and lowers the incidence of arrhythmias.
 - (ii) *Antiemetics*– an antiemetic may be given IV.
 - (iii) *Antiarrhythmics*– Arrhythmias are common in patients in acute MI; suitable antiarrhythmics should be used depending on the arrhythmia.

Long-term Treatment

Once the patient is stabilized, certain drugs are recommended for prevention of further ischaemic events. Long-term administration of low dose aspirin, a β -adrenergic blocker and an ACE inhibitor are useful in reducing long-term mortality. ACE inhibitors prevent ventricular remodelling and cardiac failure.

Risk Factor Management

- Smoking should be stopped.
- Hyperlipidaemia if any should be controlled.
- Body weight should be reduced if needed.
- Regular moderate exercises should be advised.
- Adequate control of diabetes and hypertension if any.

Dental implications: A majority of dental procedures can evoke anxiety in the patient. This could precipitate an attack of angina or rarely even myocardial infarction. Utmost importance is given to keep the patient stress-free. Adequate antianxiety agents, analgesics and anaesthetics are used to avoid pain and anxiety. Patient is taken for the procedure as the first case in the morning because waiting in anxiety could be harmful to such patients. Adrenaline is avoided in such patients. The dentist should know to handle the emergency if the need arises and then shift the patient to the physician's care at the earliest. For an acute episode of angina, nitroglycerine 0.5 mg is given sublingually immediately. The pain should subside in 3-5 minutes (See Page 107). If MI is suspected, injection pethidine 50 mg should be given immediately even before shifting the patient to the physician.

18

Antihypertensive Drugs

Hypertension is an elevation of systolic and/or diastolic BP above 140/90 mm of Hg. It is a common cardiovascular entity. Hypertension (HT) may be *primary* (essential) hypertension—where the cause is not known or *secondary*—when it is secondary to other conditions like renal, endocrine or vascular disorders.

Based on the degree of severity, hypertension can be graded as:

- Mild—diastole up to 104
- Moderate—105-114
- Severe— more than 115.

Blood pressure is determined by cardiac output (CO) and total peripheral vascular resistance (PVR). Blood pressure is controlled by baroreceptor reflexes acting through autonomic nervous system along with the renin-angiotensin-aldosterone system.

Prolonged hypertension damages the blood vessels of the heart, brain and the kidneys and may result in several complications like stroke, coronary artery disease or renal failure. Hence hypertension needs to be treated even though as such it does not generally produce obvious troublesome symptoms.

Antihypertensives act by influencing the BP regulatory systems *viz.* the autonomic system, renin-angiotensin system, calcium channels or sodium and water balance (plasma volume).

Antihypertensives may be classified as follows :

CLASSIFICATION

1. *Diuretics*
 - *Thiazides*
Hydrochlorothiazide, chlorthalidone, indapamide
 - *Loop diuretics*
Frusemide, bumetanide, torsemide
 - *K⁺ Sparing diuretics*
Spironolactone, amiloride, triamterene.
2. *Angiotensin converting enzyme inhibitors*
Captopril, enalapril, lisinopril, ramipril, perindopril, fosinopril, trandolapril, quinapril, benazepril.
3. *Angiotensin II receptor antagonists*
Losartan, candesartan, valsartan, eprosartan, irbesartan.
4. *Sympatholytics*
 - *Centrally acting drugs*
Clonidine, methyl dopa, guanabenz, guanfacine
 - *Ganglion blockers*
Trimethaphan
 - *Adrenergic neuron blockers*
Guanethidine, reserpine
 - *Adrenergic receptor blockers:*
 - *α blockers*
Prazosin, terazosin, doxazosin
 - phenoxybenzamine, Phentolamine

- β blockers
Propranolol, atenolol, esmolol, metoprolol.
- α and β blockers
Labetalol, carvedilol
- 5. Ca^{++} channel blockers
Verapamil, nifedipine, nicardipine, nimodipine, amlodipine, felodipine.
- 6. Vasodilators
 - Arteriolar dilators
Hydralazine, minoxidil, diazoxide
 - Arteriolar and venular dilators
Sodium nitroprusside.

Diuretics (see Chap. 13) The antihypertensive effect of diuretics is mild—BP falls by 15-20 mm of Hg over 2-4 weeks. Diuretics act as antihypertensives as follows.

Diuretics enhance the excretion of sodium and water resulting in

1. $\downarrow$ Plasma volume $\rightarrow \downarrow$ cardiac output $\rightarrow \downarrow$ BP
2. $\downarrow$ Body sodium $\rightarrow$ relaxation of vascular smooth muscles (due to Na^+ depletion in the vascular smooth muscle) - $\downarrow$ PVR $\rightarrow \downarrow$ BP.

Restriction of dietary salt intake will reduce the dose of the diuretic needed. Thiazides are the first-line antihypertensives and are inexpensive. An initial dose of 12.5 mg daily hydrochlorothiazide/chlorthalidone is given. If the response is not adequate the dose may be increased to a maximum of 25 mg daily. They may be combined with a K^+ sparing diuretic which is the best way to avoid hypokalaemia—1.25 mg amiloride with 12.5 mg hydrochlorothiazide. Thiazides may be used in combination with other antihypertensives particularly with those that cause salt and water retention as a side effect.

Indapamide is particularly useful in hypertension because it lowers BP in

subdiuretic doses. Moreover it causes milder electrolyte disturbances.

Loop diuretics - Although loop diuretics like frusemide are powerful diuretics, their antihypertensive efficacy is low. They are used only in hypertension with chronic renal failure or congestive heart failure.

Angiotensin Converting Enzyme (ACE) Inhibitors

Angiotensin II is a powerful vasoconstrictor. Aldosterone also raises the BP by increasing the plasma volume (Fig. 18.2). ACE inhibitors prevent the formation of angiotensin II and (indirectly) aldosterone. There is vasodilation and decrease in PVR resulting in a fall in BP. As ACE also degrades bradykinin, ACE inhibitors raise the bradykinin levels which is a potent vasodilator. This also contributes to the fall in BP.

The blood flow to the kidneys, brain and heart increases due to selective vasodilation and thus maintains adequate blood supply to these vital organs.

Pharmacokinetics ACE inhibitors are generally well-absorbed. Except captopril and lisinopril all others are prodrugs. They differ in their potency and pharmacokinetic properties (Table 18.1) like bioavailability, distribution, plasma $t_{1/2}$ and excretion. Most ACE inhibitors are excreted through the kidney $\rightarrow$ dose should be reduced in renal dysfunction.

Adverse effects ACE inhibitors are well-tolerated. Adverse effects include:

1. *Persistent dry cough* due to $\uparrow$ bradykinin levels is more common in women. It may require withdrawal of the ACE inhibitors. An angiotensin II receptor antagonist may be used in such patients (Page 114)
2. *Hypotension*—On initiation of therapy, ACE inhibitors may cause significant hypo-

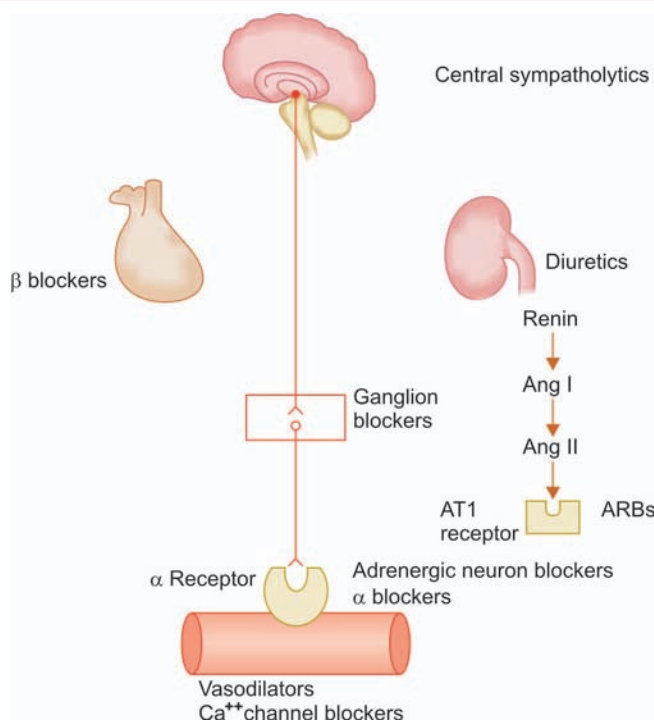


Fig. 18.1 : Sites of action of antihypertensive drugs

tension called first dose phenomenon. Hence, treatment should be started with small doses and if patients are already on diuretics - temporarily diuretics should be stopped.

3. *Hyperkalaemia*—ACE inhibitors may cause hyperkalaemia particularly in patients on K⁺ sparing diuretics or on K⁺ supplements.
4. *Dysguisia*—An altered taste sensation is more common with captopril—it is however reversible.
5. *Angioneurotic edema*—ACE inhibitors can rarely cause (0.1% incidence) angioedema with swelling in the lips, nose, larynx and airway obstruction. It may be due to increased bradykinin levels and can be fatal. ACE inhibitors should be

immediately withdrawn at the first sign of angioedema. Severe cases may need adrenaline and glucocorticoids.

6. *Skin rashes*—ACE inhibitors can occasionally cause skin rashes which are self-limiting.
7. *Teratogenicity*—Given during second and third trimester of pregnancy, ACE inhibitors can cause various foetal malformations including foetal growth retardation, malformed lungs and even death→ ACE inhibitors are contraindicated in pregnancy.
8. *Other effects*—They can cause headache, nausea, abdominal pain, proteinuria and rarely neutropenia.

Neutropenia is more common in patients with collagen diseases and should be watched for. ACE inhibitors can precipitate acute renal failure in patients with renal artery stenosis.

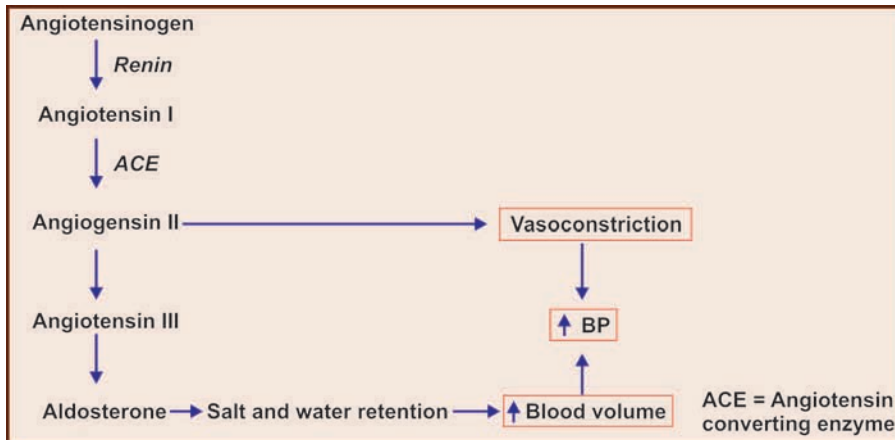


Fig 18.2: Renin-angiotensin system

Uses

1. Hypertension

- ACE inhibitors are presently the first line antihypertensives.
- ACE inhibitors are useful in the treatment of hypertension of all grades due to all causes.
- Addition of a diuretic potentiates their antihypertensive efficacy. They are generally combined with thiazides without a K⁺ sparing diuretic because there can be significant hyperkalaemia.
- They are specially indicated as antihypertensives in:
 - a. hypertension with left ventricular hypertrophy — hypertrophy is gradually reversed by ACE inhibitors.
 - b. patients with diabetes because ACE-I slow the development of nephropathy.
 - c. renal diseases with hypertension— ACE inhibitors slow the progression of chronic renal diseases like glomerulosclerosis.
 - d. patients with co-existing IHD including post-MI patients.
- ACE inhibitors are well tolerated
- In severe hypertension, they may be combined with other antihypertensives like β blockers, CCBs or diuretics.

2. CCF-ACE inhibitors are the first line drugs (see page 111).
3. *Myocardial infarction* ACE inhibitors started within 24 hours and given for several weeks prevent the development of CCF and reduce mortality.
4. *Coronary artery disease*-In patients who are at a high risk of ischaemic cardiovascular conditions like MI and stroke, ACE inhibitors afford significant benefit by reducing the risk of MI, stroke and sudden death.
5. *Chronic renal failure*-In patients with diabetic nephropathy and chronic renal failure, ACE inhibitors delay the progression of renal disease.
6. *Scleroderma renal crisis*-ACE inhibitors may be life saving in these patients.

Precautions and Contraindications

- ACE inhibitors are contraindicated in pregnancy
- ACE inhibitors should not be combined with K⁺ sparing diuretics.
- At the first sign of angioedema, ACE inhibitors should be stopped.

- They are contraindicated in patients with renal artery stenosis as they can cause renal failure in them.
- ACE inhibitors may enhance plasma levels of digoxin.

Angiotensin II Receptor Blockers (ARBs)

Losartan was the first orally effective AT₁ receptor antagonist to be developed. There are 2 subtypes of angiotensin II receptors—AT₁ and AT₂. AT₁ receptors are present in vascular and myocardial tissue, brain, kidney and adrenal glomerular cells. *Losartan* has high affinity for AT₁ receptors when compared to AT₂ receptors. By blocking AT₁ receptors, *losartan* blocks the effect of angiotensin II. It thus relaxes vascular smooth muscles, promotes salt and water excretion and reduces plasma volume.

The main advantage of ARBs over ACE inhibitors is that there is no increase in bradykinin levels and its associated adverse effects like dry cough and angioedema because angiotensin converting enzyme is not inhibited.

Many other ARBs have now been synthesized including *candesartan*, *irbesartan*, *valsartan*, *telmisartan* and *eprosartan*.

ARBs are all given orally. Their bioavailability is generally <50%. They are

all extensively protein bound and excreted by kidneys.

Adverse effects ARBs are well tolerated. They can cause hypotension and hyperkalaemia like ACE inhibitors. Angioedema is rare. ARBs are contraindicated in pregnancy because of their teratogenic potential.

Uses

1. Hypertension—ARBs are used in the treatment of hypertension in similar indications as that of ACE inhibitors as alternatives to ACE inhibitors. They can be considered as the first line drugs in hypertension. *Losartan*, *candesartan* and *irbesartan* are available in India. ARBs can be usefully combined with diuretics (Table 18.2)
2. *Cardiac failure*—ARBs may be used as alternatives to ACE inhibitors in cardiac failure. *i.e.*, in patients who poorly tolerate ACE inhibitors.

SYMPATHOLYTICS

I. Drugs Acting Centrally

Clonidine an imidazoline derivative is a selective α_2 agonist. Stimulation of α_2 receptors in the CNS (in the vasomotor centre and hypothalamus), decreases central sympathetic outflow, blocks the release of noradrenaline from the nerve terminals leading to a fall in BP and bradycardia.

Table 18.1: Dose and duration of action of some commonly used ACE inhibitors

Drug	Duration of action (in hrs)	Daily dose in hypertension (mg)
Captopril	6-12	12.5-50 mg BD
Enalapril	24	2.5-20 mg OD
Lisinopril	>24	5-40 mg OD
Ramipril	8-48	1.25-10 mg OD
Fosinopril	12-24	10-60 mg
Benazepril	12-24	10-40 mg
Perindopril	24	2-8 mg

Table 18.2: Dose and route of administration of some commonly used antihypertensives

<i>Antihypertensives</i>	<i>Daily doses</i>	<i>Routes</i>
Hydrochlorothiazide + Amiloride	12.5-25 mg + 1.25-2.5 mg daily	Oral
Losartan	50 mg OD	Oral
Clonidine	100-300 µg	Oral
Methyldopa	250-500 mg q 6-12 hr	Oral
Atenolol	25-100 mg OD	Oral
Prazosin	2-20 mg daily	Oral
Hydralazine	25-50 mg q 8-24 hr	Oral
Diazoxide	50-100 mg every 5-10 min	IV
Sodium nitroprusside	0.2-0.3 mg/min	IV
Nifedipine	10 mg 5-20 mg q 8-12 hr	SL Oral

For ACE inhibitors see Table 18.1

Adverse effects include drowsiness, dryness of mouth, nose and eyes; parotid gland swelling and pain, fluid retention, constipation and impotence. Sudden withdrawal of clonidine will lead to rebound hypertension, headache, tremors, sweating and tachycardia. Hence the dose should be tapered.

Uses

1. Mild to moderate hypertension.

Other Uses

2. In *Opioid withdrawal* Most withdrawal symptoms in opioid addicts are of sympathetic overactivity and can be benefited by treatment with clonidine.
3. *Diabetic neuropathy* Clonidine controls diarrhoea by improving absorption of sodium chloride and water in the gut by stimulation of α_2 receptors in the intestines.
4. *With anaesthetics* Clonidine given preoperatively reduces the dose of the general anaesthetic needed due to its analgesic effects.

α -methyl dopa—an analog of dopa, is a prodrug. It is metabolised in the body to *α -methylnorepinephrine* which is an α_2 agonist and acts like clonidine. Renin levels also fall. Left ventricular hypertrophy is reversed in about 12 weeks of treatment.

Adverse effects are sedation, dryness of mouth and nose, headache, postural hypotension, fluid retention and impotence.

Uses

α -methyl dopa is used in mild to moderate hypertension along with a diuretic. It is safe in hypertension during pregnancy and is the preferred antihypertensive in such patients. Started with 250 mg twice daily, the dose may be increased to a maximum of 750 mg BD.

Ganglion Blockers

Trimethaphan

These drugs block both sympathetic and parasympathetic ganglia resulting in decreased sympathetic tone and a fall in BP. But they produce several side effects as they block both sympathetic and parasympathetic ganglia and are not used

now. Trimethaphan is the only ganglion blocker in use. It is used intravenously to produce controlled hypotension during certain surgeries for its rapid and short action (15 minutes).

Adrenergic Neuron Blockers

Guanethidine depletes the stores of noradrenaline in the adrenergic neurons and also blocks its release. Because of the adverse effects like postural hypotension, diarrhoea and sexual dysfunction, it is not used.

Reserpine is an alkaloid obtained from *Rauwolfia serpentina* (Sarpagandhi) that grows in India. In the adrenergic neurons, it binds to the vesicles that store monoamines like noradrenaline, dopamine and 5-HT and destroys these vesicles. It thus depletes the stores of these monoamines and reduces BP. Reserpine also has antipsychotic effects for which it is used in psychosis. Reserpine causes various side effects like drowsiness, depression, parkinsonism, postural hypotension, edema and sexual dysfunction. Though it is generally not preferred. It has the advantages of being inexpensive, effective, long acting (once daily dose) and generally well tolerated when given with a diuretic.

Adrenergic Receptor Blockers

β -blockers (see Chapter 12) are mild antihypertensives. Blockade of cardiac β_1 receptors results in decreased myocardial contractility and cardiac output. Thus they reduce the BP due to a fall in the cardiac output. They also lower plasma renin activity and have an additional central antihypertensive action.

β blockers are effective and well-tolerated and are of special value in patients who also have arrhythmias or angina. They may be used alone but are also suitable for

combination with other antihypertensives particularly with drugs that cause tachycardia as their side effect (e.g. vasodilators). They are thus the first line antihypertensive drugs in mild to moderate hypertension. Atenolol is the preferred β -blocker because of the advantages like once a day dosing, absence of CNS side effects and β_1 selectivity. β -blockers should always be tapered while withdrawing.

α -blockers (see Chapter 12) Nonselective α blockers like phenoxybenzamine and phentolamine are used in the treatment of hypertension due to pheochromocytoma. Selective α_1 blockers like prazosin, terazosin and doxazosin dilate both arterioles and venules. Peripheral vascular resistance is decreased leading to a fall in BP with only mild tachycardia.

'First dose phenomenon' can be avoided by starting with a low dose prazosin (0.5 mg) given at bed time. Dose is gradually increased. α_1 blockers are used in mild to moderate hypertension; they may be combined with diuretics and β -blockers.

α and β -blockers Labetalol and carvedilol block α_1 and β receptors. It is used IV in the treatment of hypertension in pheochromocytoma and in hypertensive emergencies.

Calcium Channel Blockers

Calcium channel blockers (see chap 15) are another important group of antihypertensives. They dilate the arterioles resulting in reduced peripheral vascular resistance. Nifedipine produces some reflex tachycardia while this is not seen with verapamil and diltiazem as they are cardiac depressants. Fluid retention is negligible unlike other arteriolar dilators. Calcium channel blockers were earlier considered first line antihypertensives and were extensively used. But several recent large scale studies have shown them to have many disadvantages. They are

not preferred in patients who also have left ventricular hypertrophy and previous myocardial infarction. Short acting DHPs produce frequent changes in BP and sympathetic activity and hence should be avoided in hypertension.

Use in Hypertension

- CCBs are well-tolerated, and effective.
- CCBs are particularly effective in elderly patients.
- CCBs may be used as monotherapy or in moderate to severe HT along with other antihypertensives.
- It has now been shown that sublingual nifedipine does not actually achieve plasma concentration quicker than oral formulation. Thus in hypertensive emergencies, short acting DHPs can be used parenterally.
- There is a growing concern that use of CCBs, especially short acting ones, is associated with increased mortality and risk of sudden death.
- Sustained release preparations or long acting dihydropyridine CCBs may be used for smoother control of BP.

Vasodilators

Vasodilators relax the vascular smooth muscles thus reducing BP due to decreased peripheral vascular resistance. Salt and water

retention and reflex tachycardia are common with vasodilators.

Hydralazine is a directly acting arteriolar dilator. The fall in BP is associated with tachycardia, renin release and fluid retention. Coronary, cerebral and renal blood flow are increased.

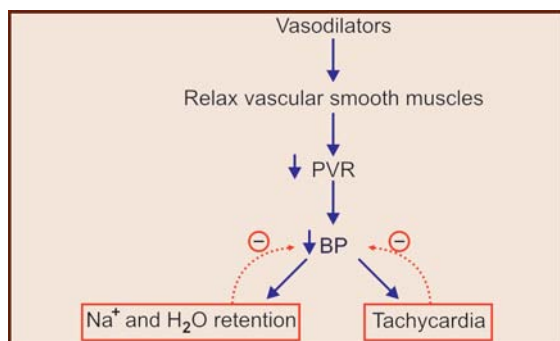
Hydralazine is metabolised by acetylation in the liver (like INH) and the rate of acetylation is genetically determined - people may be fast or slow acetylators.

Adverse effects are headache, dizziness, flushing, palpitation, nausea, hypotension and salt and water retention. It may precipitate angina in some patients because of increased O_2 demand due to reflex tachycardia and decreased myocardial blood supply due to peripheral vasodilatation. Hypersensitivity reactions like serum sickness and lupus erythematosus (arthralgia, fever, pleuritis, pericarditis) may occur and is more common in slow acetylators.

Uses Hydralazine is used with a β -blocker and/or a diuretic in moderate to severe hypertension not controlled by the first line drugs. It can be given in hypertension during pregnancy (2nd and 3rd trimester).

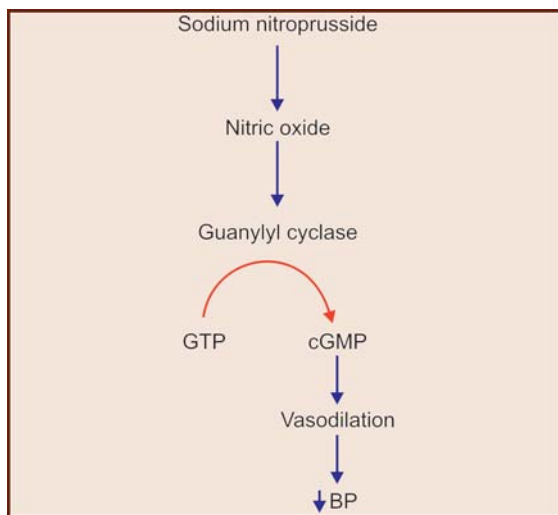
Minoxidil is a directly acting arteriolar dilator used in severe hypertension not responding to other drugs. It acts by opening K^+ channels in the smooth muscles. Opening of the K^+ channels causes efflux of K^+ resulting in hyperpolarisation and smooth muscle relaxation.

Minoxidil is used along with a diuretic - as a reserve drug in patients with severe hypertension who do not respond to other drugs. Minoxidil stimulates the growth of hair on prolonged use (hypertrichosis). Hence it is used topically (2% solution) in alopecia. Young men with relative alopecia are more likely to respond. Minoxidil can cause fluid retention, tachycardia and anginal



episodes. Growth of hair on the face, arms, legs and back make it unacceptable in women. *Diazoxide* is related to thiazide diuretics and is a potent arteriolar dilator. Its mechanism of action is like minoxidil. Diazoxide can cause hyperglycaemia because it inhibits the insulin secretion from pancreas. Other side effects include salt and water retention, palpitation and myocardial ischaemia. It is used intravenously in hypertensive emergencies where monitoring of infusion is not possible. Diazoxide has a long duration of action (24 hours) and is suitable in such situations.

Sodium nitroprusside is a rapidly acting vasodilator and it relaxes both arterioles and venules. Both peripheral resistance and cardiac output are reduced resulting in lower myocardial oxygen consumption.



Nitroprusside acts through the release of nitric oxide which activates guanylyl cyclase, resulting in the formation of cGMP which relaxes the vascular smooth muscles. On IV administration, it is rapid (acts within 30 seconds) and short-acting (duration 3 minutes) allowing titration of the dose. This makes it suitable for use in hypertensive emergencies with close monitoring. It decomposes on

exposure to light *the infusion bottle and tubing should therefore be covered with opaque foil.*

Adverse reactions are palpitation, sweating, weakness, nausea, vomiting and hypotension. In higher doses nitroprusside gets converted to cyanide and thiocyanate which can result in toxicity. Symptoms of toxicity include nausea, anorexia, weakness, disorientation and psychosis. Administration of sodium thiosulphate along with nitroprusside prevents the accumulation of cyanide.

Uses

1. Nitroprusside is the drug of choice in hypertensive emergencies.
2. It is used in situations where short-term reduction of myocardial work load is required as in myocardial infarction.

Drug Interactions

1. Sympathomimetics and tricyclic antidepressants can antagonise the effects of sympatholytics.
2. Antihistamines add to sedation produced by clonidine and methyldopa.
3. NSAIDs tend to cause salt and water retention and may blunt the effect of antihypertensives.

Treatment of Hypertension

Mild hypertension Treatment is started with low dose of a single drug—a thiazide diuretic or a β -blocker. If the patient does not adequately respond in 3-4 weeks, an ACE inhibitor or a calcium channel blocker should be tried. If BP is not controlled by one drug, another should be added.

Moderate hypertension A combination of a diuretic with a sympatholytic may be given. If response is inadequate add a third drug.

Severe hypertension may be associated with cardiac or renal disorder. A vasodilator with a diuretic and a β -blocker is useful.

Hypertensive emergencies Conditions like hypertensive encephalopathy and acute cardiac failure due to hypertension require immediate reduction of BP. Parenteral drugs are preferred. IV sodium nitroprusside under close monitoring is the drug of choice (in some conditions BP should be lowered gradually to avoid ischaemia to vital organs). IV esmolol, diazoxide and sublingual nifedipine are alternatives. BP should be constantly monitored because drugs like sodium nitroprusside can bring down BP suddenly which results in hypoperfusion of vital organs. As soon as possible switch over to oral drugs.

Hypertension in pregnancy The drugs found safe are—methyldopa orally for maintenance and hydralazine (parenteral) for reduction of BP in emergency. However they should be used only after the first trimester. Cardio-selective β -blockers (atenolol) can also be used.

Combination of antihypertensives When it is not possible to achieve adequate control of BP with a single drug, a combination may be used. Antihypertensives may also be combined to overcome the side effects of one another. This also allows use of lower doses of each drug.

Sympatholytics and vasodilators cause fluid retention which can be overcome by adding a diuretic.

Vasodilators like nifedipine and hydralazine evoke reflex tachycardia. This can be countered by β -blockers, while propranolol may cause initial rise in PVR which is countered by vasodilators.

Combination of ACE inhibitors and diuretics is synergistic.

Non-pharmacological measures Low salt diet, weight reduction and transidental meditation—all go a long way in controlling the blood pressure. Smoking and alcohol should be given up. These measures also help in reducing the dose of the antihypertensive needed.

Hypertension and Dentistry

A dentist may have to carry on surgeries and other procedures on a hypertensive patient and needs caution. It may not matter much in minor procedures but in major procedures, good control of BP should be ensured before, during and after the procedure. BP is maintained below 150/100 mm of Hg. To control postoperative bleeding ethamsylate is given. When local anaesthetic is required, for minor procedures plain lignocaine is used and adrenaline avoided. Procedures are done in multiple sittings. For example if multiple teeth are to be pulled out, 1-2 teeth are extracted at a time. If the bleeding is more, botropase or gel foam application is used and not adrenaline packs.

19 Plasma Expanders and Pharmacotherapy of Shock

PLASMA EXPANDERS

Plasma expanders are high molecular weight substances which when infused IV exert osmotic pressure and remain in the body for a long time to increase the volume of circulating fluid.

An ideal plasma expander should exert oncotic pressure comparable to plasma, be long-acting, non-antigenic and pharmacologically inert.

The plasma expanders used are dextrans, gelatin polymer, hydroxyethyl starches and polyvinyl pyrrolidone - all colloidal compounds. Human albumin obtained from pooled human plasma is also useful.

Dextrans (Dextran 70 - mol. wt. 70,000 and dextran 40 - mol. wt. 40,000) are polysaccharides obtained from sugar beet. Their osmotic pressure is similar to that of plasma proteins. Dextran 70 effectively expands the plasma volume and remains so for 24 hours. It interferes with coagulation, blood grouping and cross matching.

Dextran 40 is faster but shorter acting. It can improve microcirculation in shock by preventing rouleaux formation of RBCs and have an antisludging effect. It can clog renal tubules resulting in renal failure - though rare should be watched for. Allergic reactions are common as dextrans are antigenic.

Dextrans have a long shelf-life (10 years) and can be easily sterilized. Dextrans are the commonly used plasma expanders.

Gelatin products have a mol. wt. of 30,000 and a duration of action of 12 hours. Gelatin polymers can remain stable for almost 3 years at a pH of 7.2-7.3. They do not interfere with coagulation, blood grouping and cross matching. They can rarely cause urticaria, allergic reactions and bronchospasm.

Hydroxyethyl starch (Hetastarch) maintains blood volume for a long period. Allergic reactions are rare and it does not interfere with coagulation.

Polyvinyl pyrrolidone (PVP) is a synthetic polymer. It is not preferred due to various disadvantages like - it provokes histamine release and interferes with blood grouping. *Human albumin* is obtained from pooled human blood. It is given as 5% or 20% solution. It is nonantigenic, does not interfere with coagulation, blood grouping or cross matching.

Human albumin is used in oedema, burns, hypovolaemic shock, hypoproteinaemia, acute liver failure and in dialysis.

Allergic reactions and fever can occur though rarely.

Uses of plasma expanders These are used as plasma substitutes in hypovolaemic shock,

burns and in extensive fluid loss—as an emergency measure to restore plasma volume.

PHARMACOTHERAPY OF SHOCK

Shock is acute circulatory failure with underperfusion of tissues. Symptoms of sympathetic overactivity are generally seen—like pallor, sweating, cold extremities and tachycardia. Shock may be:

1. *Hypovolaemic shock* Decreased fluid volume due to sudden loss of plasma or blood as in haemorrhage, burns or dehydration—results in hypovolaemic shock. Fluid and electrolytes (See page 401) should be replaced and BP monitored.
2. *Septic shock* is precipitated by severe bacterial infection. It may be due to release of bacterial toxins — should be treated with appropriate antibiotics apart from general measures.
3. *Cardiogenic shock* is due to failure of heart as a pump as in myocardial infarction. IV morphine is the drug of choice to relieve pain and anxiety (see page 108).
4. *Anaphylactic shock* Type I hypersensitivity reaction causing release of massive amounts of histamine which is triggered by antigen-antibody reaction. Adrenaline 0.3–0.5 ml of 1:1000 solution given intramuscularly is the drug of choice (see page 71)
5. *Neurogenic shock* is due to venous pooling as following spinal anaesthesia, abdominal or testicular trauma.

Shock of any type needs immediate treatment:

General Measures

- a. The cause should be identified and treated
- b. Maintain BP and plasma volume
- c. Correct the acid base and electrolyte disturbances
- d. Ensure adequate urine output.

To restore the intravascular volume, the component that is lost should ideally be replaced—like plasma in burns and blood after haemorrhage. But in emergency, immediate volume replacement is important. In such situations plasma expanders and intravenous fluids are used.

Section 5

Central Nervous System

20

General Anaesthetics

General Anaesthetics are agents that bring about reversible loss of sensation and consciousness. Before 1846, alcohol, opium, packing a limb with ice and concussion, i.e. making the patient unconscious by a blow on the head were used to relieve surgical pain. Dr Horace Wells a dentist, tried to demonstrate the effect of nitrous oxide as an anaesthetic in 1844 but was unsuccessful as he removed the gas bag too early. Dr William Morton who was present at the demonstration, worked on it and in 1846 demonstrated ether anaesthesia successfully. Since then several anaesthetics have been synthesized over the decades.

Stages of General Anaesthesia

1. *Stage of analgesia* is from the beginning of inhalation of the anaesthetic to loss of consciousness.
2. *Stage of delirium* This stage is from loss of consciousness to beginning of surgical anaesthesia. It may be associated with excitement—shouting, crying and violent behaviour.
3. *Stage of surgical anaesthesia* This has 4 planes. As anaesthesia passes to deeper planes, respiratory depression is seen. There is gradual loss of reflexes and relaxation of skeletal muscles.
4. *Stage of medullary paralysis* is seen only with overdose. It is the stage of medullary

depression → cessation of breathing, circulatory failure and death may follow.

Ideal anaesthetic should be pleasant, non-irritating, provide adequate analgesia, immobility and muscle relaxation; should be non-inflammable and administration should be easy and controllable and have a wide margin of safety. Induction and recovery should be smooth and should not affect cardiovascular functions. It should be inexpensive.

Mechanism of Action of General Anaesthetics

The exact mechanism of action of general anaesthetics is not known. The most accepted mechanisms of action are as follows.

1. Inhaled and some intravenous anaesthetics bind to specific sites on GABA receptor chloride channels and activate these receptors. By this they increase the inhibitory neurotransmission and depress the CNS.
2. Inhalational anaesthetics also enhance the sensitivity of glycine-gated chloride channels to glycine. These glycine receptors bring about inhibitory neurotransmission in the brainstem.
3. Some anaesthetics like ketamine and nitrous oxide bind to and inhibit the N-methyl D – aspartate (NMDA) receptors.
4. Inhalational and intravenous agents act at multiple sites in the nervous system and depress the neuronal activity at many sites in the brain.

General anaesthetics are as follows-

CLASSIFICATION

I. Inhalational

A. Gases

- Nitrous oxide, cyclopropane

B. Liquids

- Ether, halothane, enflurane, isoflurane, methoxyflurane, desflurane, sevoflurane

II. Intravenous

A. Inducing agents

- Thiopentone sodium, methohexitone, propofol, etomidate

B. Dissociative anaesthesia

- Ketamine

C. Neuroleptanalgesia

- Fentanyl + droperidol

D. Benzodiazepines

- Diazepam, lorazepam, midazolam

Inhalational anaesthetics are either gases or volatile liquids. Given by inhalation they are absorbed by the pulmonary circulation. On attaining adequate concentration in the brain, they produce general anaesthesia.

Pharmacokinetics Inhalational anaesthetics are administered at a specific concentration. Since the brain is a highly perfused organ, steady state can be achieved quickly. When the steady state is reached, the partial pressure of the anaesthetic in the lung and the brain are equal and this makes it possible to monitor the anaesthesia. But, for anaesthetics with high solubility in blood and tissues, rise in alveolar partial pressure (and thereby induction) is slower. Such anaesthetics need to be administered at higher pressures.

Inhaled anaesthetics are largely eliminated unchanged by the lungs. Agents which are soluble in fat and tissues require longer time

for elimination and therefore recovery is slower.

Minimum alveolar concentration (MAC) is the concentration that immobilizes 50% of subjects in response to a surgical skin incision. MAC is used to describe the potencies of different volatile anaesthetics.

Nitrous oxide is a gas with a slightly sweetish odour. It produces light anaesthesia without significant depression of respiration or vasomotor centre (Table 20.1).

Advantages

1. Strong analgesic
2. Induction is rapid and smooth
3. It is non-irritating and non-inflammable
4. Recovery is rapid
5. Postoperative nausea is not significant
6. Has little effect on respiration and cardiovascular functions, hence ideal for combination
7. It is non-toxic to liver, kidney and brain and is quickly removed from lungs.

Disadvantages

1. It is less potent and should be used with other agents.
2. Poor muscle relaxant.
3. N₂O displaces nitrogen from the air-filled cavities and while doing so, it enters the cavities faster, i.e. even before nitrogen escapes. This results in expansion of such cavities like in patients with pneumothorax and air embolus. Hence N₂O should be avoided in such patients.
4. Repeated use can depress the bone marrow.
5. Long-term exposure (like in staff of operation theatre) to low doses can impair DNA synthesis which may result in foetal abnormalities on conception.

Status in anaesthesia Nitrous oxide is used as an adjuvant to other anaesthetics. It is used along with oxygen (30%).

Ether is a colourless volatile liquid. It is highly inflammable; vapours are irritating.

Advantages

1. Potent and reliable anaesthetic.
2. Good analgesic.
3. Effect on cardiovascular and respiratory functions are not significant in therapeutic doses; reflexes are well-maintained.
4. It is a bronchodilator.
5. Provides full muscle relaxation in deep anaesthesia.
6. Does not sensitize the heart to adrenaline.
7. Easy to administer as complicated equipment is not necessary.
8. Inexpensive.

Disadvantages

1. It is inflammable—hence diathermy is contraindicated.
2. Highly soluble in body tissues—induction is slow and unpleasant.
3. It is irritating and therefore enhances respiratory secretions. Premedication with atropine is essential—laryngeal spasm may occur during induction.
4. Postoperative nausea and vomiting are frequent.
5. Recovery is slow.

Status in anaesthesia Ether is now not preferred because of flammability and irritant property. But it is still used in developing countries like India because it is cheap, easy to administer (by open drop method) and relatively safe.

Halothane is a colourless volatile liquid with a sweet odour. It is non-irritant and non-inflammable.

Advantages

1. Potent, non-inflammable anaesthetic.

2. Induction is smooth and rapid—in 2-5 min surgical anaesthesia can be produced.
3. Non-irritant—therefore does not augment salivary or bronchial secretions.
4. Recovery is rapid (Table 20.2).
5. Postoperative nausea and vomiting are of low incidence.

Disadvantages

1. Neither a good analgesic nor a muscle relaxant.
2. Halothane is a direct myocardial depressant. Cardiac output and BP start falling and heart rate may decrease. It sensitizes the heart to the arrhythmogenic action of adrenaline.
3. It also causes some respiratory depression.
4. Severe hepatitis which may be fatal occurs in 1: 50,000 patients. A metabolite may be responsible for this toxicity.
5. Malignant hyperthermia—a genetically determined reaction occurs rarely. Succinylcholine accentuates this effect of halothane. It is due to intracellular release of calcium from the sarcoplasmic reticulum which causes muscle contraction and increased heat production. It is treated with dantrolene.
6. Expensive when compared to ether.

Status in anaesthesia Halothane is one of the most popular anaesthetics. Analgesics and muscle relaxants are used as adjuvants. Non-flammability, non-irritant property, rapid induction and recovery has made it an important and preferred anaesthetic—most widely used.

Enflurane is similar to halothane except that:

1. it is metabolised to a lesser extent than halothane—therefore safer regarding the liver toxicity.

2. does not sensitize the heart to adrenaline. But enflurane may precipitate seizures in epileptics and should be avoided in them.

Isoflurane is an isomer of enflurane and is similar to halothane. It differs as follows:

1. more potent than halothane.
2. does not sensitize the heart to adrenaline.
3. metabolism is negligible—therefore safer regarding the liver toxicity.
4. it does not provoke seizures.

Isoflurane is extensively used now. It is expensive and can cause hypotension.

Desflurane and sevoflurane are newer agents which allow very rapid induction and recovery because of low solubility in blood. But they too have some disadvantages. Desflurane is pungent—may induce coughing and sometimes laryngospasm. Because of low volatility, a special vapouriser is required for administration. Sevoflurane is chemically unstable and may get degraded to a compound that is nephrotoxic. A metabolite of sevoflurane

formed in the liver also may cause renal damage. If these disadvantages of sevoflurane could be overcome, we may have found an ideal anaesthetic.

Oxygen in anaesthesia Oxygen should be added routinely to inhalational agents to protect against hypoxia (especially when halothane is used). When O₂ is not available, ether is the safest agent for maintenance of anaesthesia.

INTRAVENOUS ANAESTHETICS

Intravenous anaesthetics allow an extremely rapid induction because the blood concentration can be raised rapidly—in one arm-brain circulation (~ 11 sec) there is loss of consciousness. But when we administer anaesthetics intravenously, there is no channel for quick elimination like the lungs. Moreover, elimination of inhaled anaesthetics can be hastened by inducing hyperventilation, while this is not possible with intravenous anaesthetics. Hence IV anaesthetics are used

Table 20.1: Compare and contrast nitrous oxide, ether and halothane

Features	Nitrous oxide	Ether	Halothane
State	Gas	Liquid	Liquid
Potency	Low	Good	Good
Flammability	No	Inflammable	No
Irritant property	No	Yes	No
Analgesia	Good	Good	Poor
Effect on CV function and respiration	Not significant	Not significant	Significant (Depressant)
Muscle relaxation	Poor	Good	Very poor
Risk of hepatitis	No	No	Yes
Induction and recovery	Smooth and rapid	Unpleasant and slow	Smooth and rapid
Use in anaesthesia	Used as adjuvant along with oxygen	Rarely used	Commonly used

Table 20.2: Compare and contrast halothane and thiopentone sodium

Features	Halothane	Thiopentone
1. Chemistry	Fluorinated compound	Barbiturate
2. State	liquid	liquid
3. Route of administration	Inhalation	Intravenous
4. Onset of action	In minutes	In seconds
5. Recovery	Medium	Fast (8-10 min)
6. Cardiac effect	Sensitizes heart to the effect of adrenaline	No such effects
7. Equipment for administration	Special equipment required	Not required
8. Risk of malignant hyperthermia	Present	Nil
9. Use in anaesthesia	For maintenance	For induction
10. Contraindication	Previous halothane hepatitis	Acute intermittent porphyria

for induction because of the rapid onset of action (Table 20.3) and anaesthesia is maintained by an inhalational agent.

INDUCING AGENTS

Thiopentone sodium is an ultrashort-acting barbiturate which when administered IV, rapidly induces hypnosis and anaesthesia without analgesia. It is highly water soluble. Extravasation of the solution produces intense pain, necrosis and gangrene.

On IV inj (3-5 mg/kg as a 2.5% solution) it produces unconsciousness in 20-30 sec. Duration of action is 4-7 minutes. It is highly lipid soluble and gets rapidly redistributed in the body tissues.

Advantages

Quick onset of action; induction is smooth, rapid and pleasant.

Disadvantages

- Not a good analgesic and not a muscle relaxant.
- It cannot be used alone as the dose required results in delayed recovery, respiratory and circulatory depression.
- A short period of apnoea occurs. Overdosage results in profound

respiratory depression. Artificial ventilation has to be given.

- Severe hypotension, hiccoughs may occur. Hypotension should be treated with plasma expanders, head low position and pressor agents.

Uses

Thiopentone sodium is used for induction of anaesthesia prior to administration of inhalational anaesthetics

Precautions Equipment for resuscitation should be ready.

Methohexitone is similar to thiopentone but is more potent. It is not preferred due to toxicity.

Propofol is an oily liquid; quick induction (30 sec) and recovery (4 min) is possible from a single dose. It is used for induction and maintenance for short procedures of up to 1 hour duration. The effect of a single dose is terminated by distribution. It can be used for total IV anaesthesia as continuous infusion or intermittent injection. It is particularly preferred for 'day-cases' when the patient has to be discharged the same day.

Etomidate is similar to thiopental but it differs in that -

- It is rapidly metabolised—as a result recovery is fast.
- Less cardiovascular and respiratory depression.

But it may cause -

- involuntary movements and excitatory effects during induction.
- pain at the injection site.
- adrenocortical suppression on long term use.

Etomidate is preferred for induction in patients with cardiovascular problems.

DISSOCIATIVE ANAESTHESIA

Ketamine In anaesthetic doses ketamine produces a trans-like state known as

dissociative anaesthesia characterised by intense analgesia, immobility, amnesia and a feeling of dissociation from one's own body and surroundings with or without actual loss of consciousness.

Mechanism of action—Ketamine acts by blocking the NMDA receptor which is an excitatory amino acid receptor.

Ketamine is highly lipid soluble and gets rapidly distributed into highly perfused organs and then redistributed to less vascular structures. Ketamine hydrochloride given 1-2 mg/kg slow IV or 10 mg/kg IM produces dissociative anaesthesia within 3-5 min which lasts for 10-15 min after a single injection. Amnesia lasts for 1-2 hr. Premedication with atropine is needed.

Table 20.3: Prominent features and use of intravenous anaesthetics

Drug	Prominent features	Uses
Thiopental	• Fast onset of action • CV* and respiratory depression	For induction
Propofol	• Fast onset and recovery • Pain at injection site • CV and respiratory depression	Short procedures
Etomidate	• Fast onset and recovery • Less CV and respiratory depression • Involuntary movements during induction • Suppresses adrenal steroidogenesis • Pain at injection site	For induction particularly in patients with low cardiovascular reserve
Ketamine	• Slow onset • Good analgesia and amnesia • No respiratory depression, no hypotension • ↑ BP • Hallucinations and involuntary movements during recovery	Short procedures particularly in children
Midazolam	• Slow onset and recovery • Less CV and respiratory depression	Short procedures like endoscopy, fracture reduction
Fentanyl + Droperidol	• Slow onset and recovery • Profound analgesia	Short procedures

*CV Cardiovascular

Return to 'consciousness' is gradual. Delirium with vivid dreams may be accompanied. If diazepam is administered pre- and postoperatively, delirium can be avoided. Heart rate, Cardiac output and BP are increased due to sympathetic stimulation.

Advantages

- Provides profound analgesia and amnesia; can be used as the sole agent for minor procedures
- Respiration is not depressed, does not induce hypotension
- Less likely to induce vomiting
- Pharyngeal and laryngeal reflexes are only slightly affected
- It is of particular value in children and poor-risk patients and also in asthmatic patients since it does not induce bronchospasm.

Disadvantages

- Hallucinations and involuntary movements may occur during recovery if used as a sole agent.
- May be dangerous in hypertensives as it raises the BP.
- Ketamine increases cerebral blood flow and intracranial pressure.

Contraindications Hypertension, CCF, cerebral haemorrhage, increased intracranial tension, psychiatric disorders and pregnancy before term.

Precautions Pulse and BP should be closely monitored; during recovery patients must be undisturbed and under observation.

NEUROLEPTANALGESIA

A combination of a neuroleptic (droperidol) with an analgesic (fentanyl) is used.

Fentanyl is a short-acting (30-50 min) and potent opioid analgesic (See Page 166).

Droperidol is a rapidly acting, potent neuroleptic related to haloperidol.

When the combination is given IV, a state of neuroleptanalgesia is produced. This is characterised by quiescence, psychic indifference and intense analgesia without loss of consciousness. It lasts for 30-40 min. Fentanyl 0.05 mg + droperidol 2.5 mg/ml – 4 to 6 ml of the solution is infused IV over 10 min. Patient is drowsy but cooperative. Respiratory depression is present. There is a slight fall in BP and HR (vagal stimulation). During recovery extra pyramidal symptoms may be seen—due to droperidol. It is employed for endoscopies, burn dressing, angiographies and other diagnostic and minor surgical procedures.

Neuroleptanaesthesia Addition of 65% N₂O + 35% O₂ to the above combination produces neuroleptanaesthesia.

BENZODIAZEPINES

Benzodiazepines like diazepam, lorazepam and midazolam are used to induce or supplement anaesthesia. They cause sedation, amnesia and reduce anxiety which are beneficial in such patients. BZDs may be employed alone in procedures like endoscopies, reduction of fractures, cardiac catheterisation and cardioversion. IV midazolam is particularly preferred as it is faster and shorter-acting, more potent, does not cause significant respiratory and cardiovascular depression and does not cause pain or irritation at the injection sites. BZDs are also used as preanaesthetic medication.

Dentistry and general anaesthesia—Though several dental procedures require general anaesthesia, they are usually administered by an anaesthetist.

PREANAESTHETIC MEDICATION

Prior to anaesthesia, certain drugs are administered in order to make anaesthesia safer and more pleasant and is known as preanaesthetic medication. It is given in order to:

1. decrease anxiety

2. provide amnesia for the preoperative period
3. relieve preoperative pain if present
4. make anaesthesia safer
5. reduce side effects of anaesthetics
6. reduce gastric acidity.

To achieve the above purpose, more than one drug is required. An informative, supportive, preoperative visit by the anaesthesiologist is very much essential.

Sedative hypnotics Antianxiety agents like benzodiazepines are used extensively as preanaesthetic medication. They reduce anxiety and produce sedation. Diazepam 5–10 mg is given orally. It also produces amnesia. Barbiturates are not preferred due to the disadvantages like respiratory depression.

Antihistamines have sedative, antiemetic and anticholinergic properties and are useful, e.g. promethazine.

Antiemetics Metoclopramide, domperidone or ondansetron may be used. Antihistamines with antiemetic properties may also be used.

Anticholinergic drugs Some irritant anaesthetics like ether increase the salivary and respiratory secretions. The secretions from the oral cavity and trachea may creep into the larynx inducing laryngospasm. They may enter into the lungs causing aspiration pneumonia. This indicated the need for drugs that reduce secretions. Fortunately we now have less irritant anaesthetics and secretions are less of a problem. Atropine 0.6 mg IM or scopolamine 0.6 mg IM or glycopyrrolate — can be used.

They

- reduce the secretions
- prevent bradycardia due to vagal stimulation

- prevent laryngospasm which is due to excessive secretions.

Scopolamine produces more sedation.

Glycopyrrolate—as compared to atropine, glycopyrrolate is longer acting, is a better antisialogogue and is less likely to cause significant tachycardia. It also produces less sedation than scopolamine.

Drugs that reduce acidity General anaesthetics may induce vomiting. This is associated with an increased risk of aspiration into the respiratory tract because normal protective airway reflexes are blunted by anaesthetics. Aspiration of the acidic gastric contents into the lungs cause damage to the lungs. H₂ blockers like ranitidine decrease gastric acid secretion and are given on the night before surgery. Decrease in gastric secretions reduces the damage to lungs if aspiration occurs while on anaesthesia.

Gastrokinetic agents metoclopramide is a dopamine antagonist that promotes gastrointestinal motility and increases the tone of oesophageal end of the stomach. This speeds gastric emptying. The combination of H₂ blocker + metoclopramide provides best protection against aspiration.

Opioids like morphine and pethidine reduce anxiety and apprehension, provide analgesia and reduce the dose of the anaesthetic required. But they depress respiration and may cause hypotension, postoperative constipation, and urinary retention; precipitate asthma and delay recovery.

Balanced Anaesthesia

Since it is not possible to achieve ideal anaesthesia with a single drug, multiple drugs are employed to attain this—preanaesthetic medication, IV anaesthetics for induction, inhalational agents for maintenance, oxygen, skeletal muscle relaxants and analgesics. This is termed *balanced anaesthesia*.

21

Local Anaesthetics

Local anaesthetics are drugs that block nerve conduction when applied locally to nerve tissue in appropriate concentrations. Their action is completely reversible. They act on every type of nerve fibre and can cause both sensory and motor paralysis in the innervated area. They act on axons, cell body, dendrites, synapses and other excitable membranes that utilize sodium channels as the primary means of action potential generation.

Cocaine was the first agent to be isolated by Niemann in 1860. In spite of its addiction potential, cocaine was used for 30 years as a surface anaesthetic. In an effort made to improve the properties of cocaine, procaine was synthesized in 1905. It ruled the field for the next 50 years. In 1943, lignocaine was synthesized and it continues to dominate the field till today.

Classification of local anaesthetics (LAs) based on the route of administration and duration of action is as follows.

CLASSIFICATION

I. *Injectable*

1. *Short-acting*
Procaine, chlorprocaine
2. *Intermediate-acting*
Lignocaine, prilocaine
3. *Long-acting*
Tetracaine (amethocaine), bupivacaine, dibucaine, ropivacaine, etidocaine.

II. *Surface anaesthetics*

Lignocaine, cocaine, tetracaine, benzocaine, oxethazaine.

Chemistry

Local anaesthetics are bases and consist of a hydrophilic amino group on one side and a lipophilic aromatic residue on the other, joined by an intermediate chain through an ester or amide linkage. Since ester links are more prone to hydrolysis than amide links, generally esters have a shorter duration of action. Depending on the linkage, LAs can be classified as:

- Ester Linked
 - Cocaine, procaine, tetracaine, benzocaine, chlorprocaine
- Amide Linked
 - Lignocaine (Lidocaine), mepivacaine, bupivacaine, etidocaine, prilocaine, ropivacaine

Since local anaesthetics are weak bases and the infected tissues have a low extracellular pH, LA ionise in such medium and a very low fraction of non-ionised LA is available for diffusion into the cell. Therefore LAs are much less effective in infected tissues.

Mechanism of Action

Local anaesthetics prevent the generation and the conduction of nerve impulses (Fig. 21.1).

The primary mechanism of action is blockade of voltage-gated sodium channels.

Local anaesthetics diffuse through the cell membrane and bind to the voltage-sensitive sodium channels from the inner side of the cell membrane. They prevent the increase in permeability to Na^+ and gradually raise the threshold for excitation. With increasing concentration, impulse conduction slows, rate of rise of action potential (AP) declines, AP amplitude decreases and finally the ability to generate an AP is abolished. These result from binding of LA to more and more sodium channels. Thus they prevent the generation of an AP and its conduction.

Small nerve fibres are more susceptible as they present a greater surface area per unit volume. Thus smaller fibres are blocked first—autonomic fibres are blocked first followed by sensory fibres conducting pain, temperature sense, then touch, pressure and vibration sensations in the same order. This is called differential blockade. Sensory and motor fibres are equally sensitive. Non-myelinated fibres are blocked more readily than the myelinated.

Addition of a vasoconstrictor like adrenaline (1:1,00,000 to 1: 2,00,000) or phenylephrine (1:20,000):

1. prolongs the duration of action of LAs by slowing the rate of absorption from the site of administration.
2. reduces systemic toxicity of LAs since the absorption rate is reduced and as it gets absorbed, it gets metabolised.

ACTIONS

Systemic Actions

Depending on the concentration attained in the plasma, any LA can produce systemic effects. LAs interfere with the functions of all organs in which conduction or transmission of impulses occur. Thus CNS, autonomic ganglia, NMJ and all muscles are affected.

CNS local anaesthetics depress the cortical inhibitory pathway thereby allowing unopposed activity of excitatory components. This loss of inhibition is manifested as restlessness, tremors and may proceed to convulsions. This central stimulation is followed by generalised CNS depression and death may result from respiratory failure.

CVS The primary site of action is the myocardium. Lignocaine decreases excitability, conduction rate and force of contraction (quinidine like effects). They also cause arteriolar dilatation. Since procaine is short-acting, procainamide is used as an antiarrhythmic. Bupivacaine is more cardiotoxic than other LAs.

Smooth muscle LAs depress contractions in the intact bowel. They also relax vascular and bronchial smooth muscles.

Pharmacokinetics

Local anaesthetics are rapidly absorbed from the mucous membranes and abraded skin. Rate of absorption is dependent on the vascularity of the area. Thus vasoconstriction decreases the absorption. Toxicity depends on the balance between absorption and metabolism, i.e. if it gets metabolised as it gets absorbed, then toxicity is less. Binding to tissues decreases the concentration in systemic circulation and thereby toxicity. Esterlinked LAs are rapidly hydrolysed by

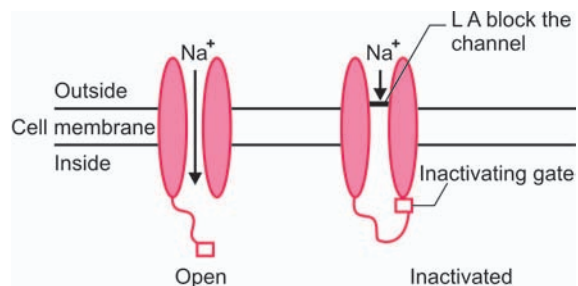


Fig 21.1: Mechanism of action of local anaesthetics. In the open state the Na^+ moves in and within milliseconds the channel is inactivated due to closure of the inactivating gate. LA block the sodium channels.

plasma pseudocholinesterase and in the liver. Amide-linked LAs are metabolised by the liver microsomes by dealkylation and hydrolysis and are not effective orally (as antiarrhythmics). They undergo extensive first pass metabolism.

Adverse Effects (Table 21.1)

1. *Hypersensitivity reactions*– include skin rashes, dermatitis, asthma or rarely anaphylaxis. These reactions are more common with ester type of drugs. Ester type LA are metabolised to PABA derivatives. These are responsible for allergic reactions while with amides, allergy is rare. Intradermal sensitivity test should be done before using these drugs. Drugs needed to manage such reactions should be kept ready. Moreover, allergy is most often due to the preservative methylparaben. Preparations that do not contain this preservative are now available.
2. *CNS*–Dizziness, auditory and visual disturbances, mental confusion, disorientation, anxiety, muscle tremors, convulsions and respiratory failure can result from large doses. Intravenous diazepam controls convulsions. Infact, these can be prevented by preanaesthetic administration of diazepam (1-2 mg/kg), especially if large doses are to be used.
3. *CVS*–Hypotension, bradycardia and arrhythmias may be encountered. Rarely cardiac arrest can occur.
4. *Local irritation*–can be seen with bupivacaine. Wound healing may be delayed.

Individual Compounds

A. Injectable (Table 21.2)

1. *Lignocaine* is the most widely used LA. It is fast and long-acting. It is useful for all types of blocks. Maximum anaesthetic effect is seen in 2-5 minutes and lasts for 30-45 minutes. In contrast to other LAs, lignocaine causes drowsiness and mental clouding. Though it is a good corneal anaesthetic, it is not generally preferred because it causes irritation. Lignocaine (XYLOCAINE) is available as 4% topical solution, 2% jelly, 5% ointment, 1% and 2% injection, 5% for spinal anaesthesia and 10% spray. Though lignocaine can be used on the eye for surface anaesthesia, it is not preferred because it causes some irritation.
2. *Bupivacaine HCl*–widely used. However, it can cause more cardiotoxicity than others. Injection 0.25-0.5% with or without adrenaline. Levobupivacaine hydrochloride is a derivative of bupivacaine that seems to be less neurotoxic and less cardiotoxic than bupivacaine.
3. *Ropivacaine*–is similar to bupivacaine except that it is less cardiotoxic.
4. *Chloroprocaine HCl*–potency is twice that of procaine and its toxicity is lower because of its more rapid metabolism.
5. *Etidocaine HCl*–its analgesic action lasts 2-3 times longer. It is used for epidural and all types of infiltration and regional anaesthesia.

Table 21.1: Adverse effects of local anaesthetics

CNS	: Dizziness, confusion, anxiety, tremors, occasionally convulsions and respiratory depression
CVS	: Hypotension, bradycardia, arrhythmias
Hypersensitivity reactions	: Rashes, dermatitis, asthma, rarely anaphylaxis

Table 21.2: Preparations and uses of some local anaesthetics

Drug	Preparation	Uses
1. Tetracaine	1-2% ointment, eyedrops, cream, powder, 0.25, 0.5% inj	Topical, spinal anaesthesia
2. Lignocaine	2-4% drops, spray, jelly, ointment, cream, 1-10% inj	Topical, infiltration, nerve block, spinal, epidural and IV regional anaesthesia
3. Benzocaine	1-2% dusting powder, 5% suppository, cream, gels, ointments, 20% spray	Topical anaesthesia
4. Oxethazaine	0.2% suspension	Topical anaesthesia (used in peptic ulcer)
5. Prilocaine	5% cream, 4% inj	Topical, nerve block anaesthesia
6. Dibucaine	0.5-1% cream	Topical anaesthesia
7. Mepivacaine	1-3% inj	Nerve block, epidural anaesthesia
8. Bupivacaine	0.25-0.75% inj	Infiltration, nerve block, spinal, epidural anaesthesia
9. Ropivacaine	2-10% inj	Infiltration, nerve block, spinal, epidural anaesthesia
10. Etidocaine	1% inj	Epidural anaesthesia

6. *Mepivacaine*—action is more rapid in onset and more prolonged than that of lignocaine.
7. *Prilocaine HCl*—onset of action and duration are longer. Because of its toxicity, its use is restricted to dental procedures.
8. *Cocaine*—(Table 21.3) produces euphoria and is a drug of dependence and abuse. It is a surface anaesthetic. It is a protoplasmic poison and hence cannot be injected. Cocaine was used for ocular anaesthesia earlier. But it causes

- constriction of conjunctival vessels, clouding and sometimes corneal sloughing and is therefore not preferred on the eye. Cocaine is used topically for anaesthesia of upper respiratory tract. It has the advantage of being a vasoconstrictor and a local anaesthetic—both in one.
9. *Procaine*—was widely used once. But is now replaced by other agents (Table 21.4). It is hydrolysed to PABA which interferes with antimicrobial activity of sulfonamides. It is rapidly absorbed

Table 21.3: Compare and contrast procaine and cocaine

Features	Procaine	Cocaine
1. Source	Synthetic	Natural— <i>Erythroxylon coca</i>
2. Chemistry	Both are esters	
3. Euphoria	Nil	Produces
4. Abuse potential	Nil	Abused since centuries
5. C.V. effects	↓cardiac contraction → ↓BP	Vasoconstriction → hypertension, arrhythmias
6. Surface anaesthesia	Does not produce	Surface anaesthetic
7. Ocular anaesthesia	Not useful	Useful—was used earlier
8. IV use	Injected IV	Protoplasmic poison—cannot be injected IV

Table 21.4: Compare and contrast procaine and lignocaine

Features	Procaine	Lignocaine
1. Chemistry	Ester	Amide
2. Distribution	Not good; rapidly excreted.	Widely distributed
3. Metabolism	Metabolised rapidly in blood	Metabolised in liver
4. In liver disease	Can be used	Toxicity likely
5. Allergic reaction	Ester type – allergy more likely	Amide – allergy less common
6. Penetrability	Poor	Good
7. Surface anaesthesia	Not a surface anaesthetic	Surface anaesthetic
8. Use	Not preferred	Most commonly used

following parenteral administration. It is ineffective when applied topically—thus not useful as a surface anaesthetic.

10. *Tetracaine*—is a PABA derivative and is 10 times more toxic and more active than procaine. It is used on the eye as 0.5% drops, ointment 0.5% and cream 1% for topical use. 0.25 to 0.5% injection is used for spinal anaesthesia.

B. Local anaesthetics used only on the eye

Benoxinate HCl—within 60 seconds of administration it produces corneal anaesthesia enough to perform tonometry. *Proparacaine HCl*—produces little or no initial irritation—0.5% ophthalmic solution is used.

C. Local anaesthetics used on the skin and mucous membranes

LAs used on the skin and mucous membranes are dibucaine, dyclonine hydrochloride and pramoxine hydrochloride. These drugs are effective when used topically in the symptomatic relief of anal and genital pruritus, poison ivy rashes, acute and chronic dermatoses. Dibucaine is the most potent, most toxic and longest-acting LA. It is available as cream and ointment.

Corneal anaesthetics used clinically

Tetracaine	Benoxinate
Lignocaine	Proparacaine

D. Poorly soluble anaesthetics

These are too slowly absorbed to be toxic. They can be applied to wounds directly and ulcerated surfaces as they produce sustained anaesthetic effect, e.g. benzocaine. Benzocaine is a PABA derivative. It is poorly soluble in water because of which it remains at the site for a longer time and toxicity is low because absorption is poor. It is used topically to anaesthetise the skin and mucous membrane.

USES OF LOCAL ANAESTHETICS

Local anaesthesia is the loss of sensation without the loss of consciousness or impairment of central control of vital functions. Depending on the site and technique of administration, LA can be:

Surface Anaesthesia

Anaesthesia of mucous membrane of the eye, nose, mouth, tracheobronchial tree, oesophagus and genitourinary tract can be produced by direct application of the anaesthetic solution. Tetracaine 2%, lignocaine 2-10% are most often used. Phenylephrine (but not adrenaline because its penetration is poor) produces vasoconstriction on topical application and prolongs duration of action.

Anaesthesia is entirely superficial and does not extend to submucosal structures. But LAs are absorbed from mucous membranes and

may result in systemic toxicity. Patient should be cautioned to expectorate the excess solution to avoid excess absorption. Local anaesthetics can also be used on abraded skin. Surface anaesthesia is useful.

1. On the eye
 - (a) for tonometry, surgery
 - (b) to remove foreign bodies from the cornea and conjunctiva
 - (c) for preoperative preparation

2. Others

Nasal lesions, stomatitis, sore throat, tonsillectomy, endoscopies, intubation, gastric ulcer, burns and proctoscopy.

An *eutectic mixture* containing 2.5% each of lignocaine and prilocaine at room temperature has a lower melting point than either of the drugs. This is emulsified and applied as a cream to anaesthetise the intact skin. The cream should be applied on the skin under an occlusive dressing and can produce anaesthesia upto a depth of 5 mm. It can be used for procedures like venipuncture and skin graft harvesting.

Infiltration Anaesthesia

Injection of a local anaesthetic solution directly into the tissue can be (i) superficial—only into the skin, or (ii) into deeper structures including intra-abdominal organs. Duration can be doubled by adrenaline (1:2,00,000). Adrenaline should not be used (i) around end arteries to avoid necrosis, and (ii) intracutaneously to avoid sloughing. Drugs used are lignocaine, procaine, bupivacaine.

Advantage By using infiltration anaesthesia, it is possible to provide anaesthesia without disruption of normal bodily functions.

Disadvantage In major surgeries—systemic toxicity due to local anaesthetic is likely as large amounts of the anaesthetic is required for such procedures.

Uses For minor procedures like incisions, drainage of an abscess, excision, etc.

Field Block

Subcutaneous injection of a LA solution proximal to the site to be anaesthetised, interrupts nerve transmission in the region distal to the injection. Sites such as forearm, scalp, anterior abdominal wall and lower extremity are used for field block. Knowledge of the relevant neuroanatomy is essential.

Advantage Lesser dose can be used to provide a greater area of anaesthesia.

Nerve Block

Injection of a solution of a LA about/around individual peripheral nerves or nerve plexuses produces larger areas of anaesthesia with a smaller amount of the drug than the above techniques. Anaesthesia starts a few centimeters distal to the injection.

Nerve block anaesthesia is useful for:

1. blocks of brachial plexus for procedures on the arm (distal to deltoid).
2. intercostal nerve blocks to anaesthetise anterior abdominal wall.
3. cervical plexus block for surgery of the neck.
4. sciatic and femoral nerve blocks for surgeries distal to the knee.
5. blocks of nerves at wrist and ankle.
6. radial and ulnar nerve block at the elbow.
7. sensory cranial nerves block.
8. facial and lingual nerves block.
9. inferior alveolar nerve block for extraction of lower jaw teeth.

Onset of action is within 3 minutes with lignocaine. Duration depends on lipid solubility and protein binding. Anaesthesia lasts longer than by field block or infiltration techniques. Nerve blocks are done for tooth extraction, operations on the eye, limbs and in neuralgias.

Spinal Anaesthesia (SA)

Local anaesthetic solution is injected into the subarachnoid space between L2-3 or L3-4

below the lower end of the spinal cord. The drug acts on nerve roots. Lower abdomen and lower limbs are anaesthetised and paralysed. The level of anaesthesia can be altered by the volume of injection, specific gravity of the solution and posture of the patient. Generally a hyperbaric solution (in 10% glucose) is injected. Isobaric and hypobaric solutions can also be given. Level of sympathetic block produced is two segments higher and motor paralysis two segments lower than sensory or cutaneous anaesthesia. Duration depends on the concentration, dose and the drug itself. Lignocaine, tetracaine, bupivacaine and ropivacaine are used for spinal anaesthesia.

Advantages

Safer, affords good analgesia and muscle relaxation and there is no loss of consciousness. In cardiac, pulmonary and renal diseases, SA may be preferred over general anaesthesia whenever possible.

Uses

Surgical procedures on the lower limb, pelvis, lower abdomen, obstetric procedures, caesarean section and other operations are done on spinal anaesthesia.

Complications of SA

1. *Hypotension and bradycardia*—sympathetic blockade results in venous pooling of the blood leading to decreased venous return, decreased cardiac output and hypotension.
2. *Respiratory paralysis*—hypotension and ischaemia of the respiratory centre results in respiratory failure. Due to paralysis of the abdominal muscles, cough reflex is less effective resulting in stasis of respiratory secretions leading to respiratory infections.
3. *Headache* due to seepage of CSF can be treated with analgesics.

4. *Cauda equina syndrome* is uncommon—control over bladder and bowel sphincters is lost because of damage to nerve roots.
5. *Sepsis*—resulting in meningitis
6. *Nausea and vomiting*—premedication can be given to prevent this.

Epidural Anaesthesia

LA is injected into the spinal extradural space. It acts on nerve roots while small amounts diffuse into subarachnoid space. It is technically more difficult and comparatively larger volumes of the anaesthetic are needed. After repeated injections tachyphylaxis may develop.

Advantages

1. Sensory blockade is 4-5 segments higher than motor blockade. This difference is useful for obstetric analgesia, as the mother has painless labour and can still cooperate in the process of labour and is conscious throughout.
2. As there is no risk of injecting into subarachnoid space, there are no chances of infection.

Intravenous Regional Anaesthesia

This type of anaesthesia is useful for rapid anaesthetization of an extremity. A rubber bandage is used to force the blood out of the limb (veins) and a tourniquet is applied to prevent the re-entry of the blood. A dilute solution of the local anaesthetic is then injected intravenously. It diffuses into extravascular tissues. Onset of anaesthesia is in 2 minutes. Because of the pain produced by the tourniquet, this type of anaesthesia is used for procedures lasting less than one hour. About 25% of the drug enters into the systemic circulation. This type of anaesthesia is commonly used on the upper limbs though it can also be used on the legs and the thighs.

Sedative Hypnotics

Sedative is a drug that produces a calming or quietening effect and reduces excitement. It may induce drowsiness. *Hypnotic* is a drug that induces sleep resembling natural sleep. Both sedation and hypnosis may be considered as different grades of CNS depression.

All human beings need sleep. Insomnia is sleeplessness. Approximately 1/3rd of our life is spent in sleep. Since centuries man has sought the help of drugs and other remedies for insomnia.

Sleep can be classified into two types depending on the physiological characteristics -

1. Non-rapid eye movement (NREM)-sleep
2. Rapid eye movement sleep (REM).

Throughout the night, NREM and REM sleep cycles repeat alternately for brief periods.

CLASSIFICATION

1. Benzodiazepines

- *Long-acting* (24-48 hours)
 - Diazepam
 - Chlordiazepoxide
 - Clonazepam
 - Flurazepam
 - Chlorazepate
 - Clobazam
- *Short-acting* (12-24 hours)
 - Temazepam
 - Lorazepam

Oxazepam
Nitrazepam
Alprazolam
Halazepam.

- *Ultra short acting* (< 6 hours)
 - Triazolam,
 - Midazolam
- 2. *Newer agents*
 - Zolpidem
 - Zopiclone
 - Zaleplon
- 3. *Barbiturates*
 - Phenobarbitone
 - Mephobarbitone
 - Secobarbitone
 - Pentobarbitone
 - Thiopentone
 - Hexobarbitone
- 4. *Miscellaneous*
 - Paraldehyde
 - Chloral hydrate
 - Glutethimide
 - Meproamate

BENZODIAZEPINES (BZD)

Chlordiazepoxide was the first BZD to be introduced into clinical medicine in 1961 and since then thousands of BZDs have been synthesized of which about 35 are now in clinical use.

Pharmacological actions The most important actions of BZDs are on the CNS and include:

1. Sedation and hypnosis
2. Reduction in anxiety
3. Muscle relaxation
4. Anticonvulsant effects
5. Amnesia.

Sedation and hypnosis BZDs hasten the onset of sleep and increase the duration of sleep. The quality of sleep resembles natural sleep more closely when compared to other hypnotics. Tolerance develops to this effect gradually.

Anxiolytic or antianxiety effects BZDs reduce anxiety and aggression and thus produce a calming effect. Alprazolam has additional antidepressant properties.

Muscle relaxant action BZDs reduce muscle tone by a central action. Generally anxiety is associated with an increased muscle tone and may be responsible for aches and pains in these patients. The muscle relaxation by BZDs adds to its beneficial effects in such patients (See page 64).

Anticonvulsant effects BZDs increase the seizure threshold and act as anticonvulsants. Diazepam is used intravenously for the treatment of status epilepticus. Other BZDs like clonazepam are used in the treatment of absence seizures and myoclonic seizures in children (See page 151).

Amnesia BZDs produce anterograde amnesia, i.e. loss of memory for the events happening

after the administration of BZDs. This property is an advantage when BZDs are used in surgical procedures as the patient does not remember the unpleasant events.

Other actions In higher doses BZDs decrease BP and increase heart rate. Diazepam decreases nocturnal gastric acid secretion.

Mechanism of Action

Benzodiazepines bind to the GABA_A receptor (Fig. 22.1) at a site which is different from the GABA-binding site. They enhance the affinity of GABA for the receptor and modulate the effects of GABA. BZDs bind to the receptor and increase the frequency of chloride channel opening. This in turn leads to increased flow of chloride ions into the neurons, resulting in hyperpolarization.

BZDs as hypnotics – when compared to barbiturates:

1. BZDs induce sleep which more closely resembles natural sleep and has less hangover.
2. In hypnotic doses they do not affect respiration or cardiovascular functions.

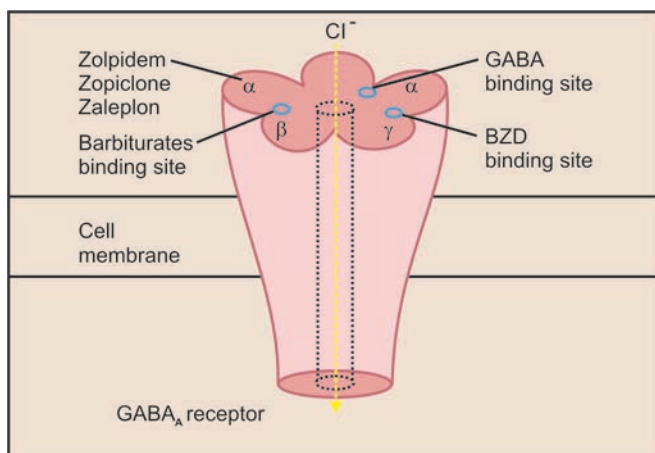


Fig. 22.1: GABA_A receptor is a pentamer made of 5 subunits (2α, 2β and 1γ). BZDs, GABA, barbiturates and newer non-BZD agents bind to different sites on the GABA_A receptor to facilitate the opening of the Cl⁻ channel. Binding of agonists opens the Cl⁻ ion channels. β carbolines bind to the BZD receptors and produce opposite effects (inverse agonists).

3. BZDs have a higher safety margin and are safer than barbiturates even in overdoses. The respiratory depression in overdoses is milder.
4. In case of BZD overdosage, a specific BZD antagonist–flumazenil can be used to reverse the symptoms.
5. BZDs do not cause microsomal enzyme induction and therefore do not alter the blood levels of other drugs.
6. BZDs have lower abuse liability.

Because of the above reasons, BZDs are the most preferred sedative hypnotics.

Pharmacokinetics There are significant pharmacokinetic differences among BZDs due to their difference in lipid solubility. BZDs are completely absorbed on oral administration. Intramuscular absorption is slow - hence oral route is preferred. They are extensively bound to plasma proteins, metabolised in the liver by glucuronide conjugation. Many BZDs particularly long acting ones are converted to metabolites which are active - thereby prolonging their

effects. For doses and duration of action see Table 22.1.

Adverse effects BZDs are generally well tolerated. The common side effects include drowsiness, confusion, amnesia, lethargy, weakness, headache, blurred vision, ataxia, day time sedation and impaired motor coordination such as driving skills—therefore, while on BZDs driving should be avoided.

In some patients it may cause paradoxical irritability and anxiety.

Tolerance and dependence Both tolerance and dependence liability are less with BZDs as compared to barbiturates. Patients develop tolerance to the sedative effects very slowly.

The withdrawal symptoms are milder and slower in onset because of the longer plasma half-life of most BZDs, but they may be abrupt and more intensive with short-acting agents. Withdrawal symptoms include anxiety, nervousness, tremors, dizziness and anorexia. When given to a pregnant mother during labour, BZDs cause hypotonia and respiratory depression in the neonate.

Table 22.1: Dose and duration of action of some commonly used hypnotics

<i>Hypnotic</i>	<i>Hypnotic dose (mg)</i>	<i>Duration of action (hrs)</i>
<i>Long acting</i>		
Diazepam	5-10	24-48
Chlordiazepoxide	10-20	24-48
Nitrazepam	5-10	24
Alprazolam	0.25-0.5	24
<i>Short acting</i>		
Triazolam	0.125-0.25	<6
Midazolam	7.5-10	<6
Lorazepam	1-2	12-18
Temazepam	10-20	12-18
<i>Newer agents</i>		
Zolpidem	5-10	<4
Zaleplon	5-20	<4
Zopiclone	7.5-10	<4

Acute overdose—BZD overdose induces sleep but the respiratory depression is mild. Hence BZDs are safe and the availability of a specific antagonist- flumazenil- makes it safer to use BZDs because poisoning can be treated.

Uses of BZDs

1. *Insomnia* When drugs are to be used to treat insomnia, BZDs are the agents of choice. Lorazepam, oxazepam, temazepam, nitrazepam or triazolam may be used.
2. *In anxiety states* BZDs are the most commonly used anxiolytics for the treatment of anxiety states and anxiety neuroses (see Page 194). Any of the BZDs except the ultra short acting ones may be used.
3. *As anticonvulsants* IV diazepam is the drug of choice in the treatment of status epilepticus. Clonazepam or clobazam are used as adjuncts with other anti-epileptic drugs (Page 151).
4. *Muscle relaxant* BZDs are centrally acting muscle relaxants used in chronic muscle spasm and spasticity.
5. *As preanaesthetic medication*—for their sedation and anxiolytic effects BZDs are useful (Page 128).
6. *During alcohol withdrawal*—BZDs are useful in patients during withdrawal of alcohol or other sedative-hypnotics.

BENZODIAZEPINE ANTAGONIST

Flumazenil is a BZD receptor antagonist which competes with BZDs for the receptor. Given intravenously flumazenil is rapid and short acting. It may rarely induce seizures.

Uses

1. To reverse BZD sedation/anaesthesia
2. In BZD overdose.

NEWER AGENTS

Newer agents include zolpidem, zopiclone and zaleplon.

- They are not BZDs but produce their effects by binding to benzodiazepine site on the GABA_A receptors and facilitate the inhibitory actions of GABA.
- They are all rapid and short acting agents and produce minimum hangover.
- Their actions are blocked by flumazenil.
- They are used for short periods when short acting hypnotics are needed.

Zolpidem is a good hypnotic but has weak anticonvulsant and muscle relaxant effects. It is short acting ($t_{1/2}$ - 2 hours) but the effects on sleep continue for a long time even after stopping zolpidem.

It is well absorbed from the gut and metabolized in the liver. Dose should be reduced in hepatic dysfunction.

Zaleplon is rapidly absorbed from the gut and has a short $t_{1/2}$ of about 1 hour. It is metabolised in the liver. It has the advantages that no withdrawal symptoms are reported after stopping it and no tolerance develops. It has rapid onset and short duration of action. No side effects are reported.

Zopiclone is another newly introduced hypnotic. Its actions resemble those of BZDs.

BARBITURATES

Barbiturates are derivatives of barbituric acid and were the largest group of hypnotics in clinical use until the 1960s.

Classification

Barbiturates can be classified based on their duration of action as:

- *Long-acting*
Phenobarbitone, Mephobarbitone

- *Short-acting*
Pentobarbitone, Butobarbitone
- *Ultrashort-acting*
Thiopentone, Hexobarbitone,
Methohexitone

Mechanism of Action

Barbiturates bind to a specific site on the GABA receptor Cl^- channel complex. They facilitate inhibitory neurotransmission by opening chloride ion channels and hyperpolarise the neural membrane.

Pharmacological Actions

1. *CNS* Barbiturates cause depression of all excitable tissues of which CNS is the most sensitive.

Sedation and hypnosis In hypnotic doses, barbiturates induce sleep and prolong the duration of sleep. The REM-NREM sleep cycle is altered with decreased duration of REM and prolonged NREM sleep. On waking up there is hangover with headache and residual sedation.

Barbiturates reduce anxiety, impair short-term memory and judgement. They can produce euphoria and are drugs of addiction while some people may experience dysphoria. Barbiturates produce hyperalgesia (increased sensitivity to pain). Therefore barbiturates, when given as hypnotics for a patient in pain may be more troublesome than being of any benefit.

Anaesthesia In higher doses barbiturates produce general anaesthesia. The ultrashort-acting barbiturates are used intravenously for this effect.

Anticonvulsant effects All barbiturates have anticonvulsant actions. Phenobarbitone and mephobarbitone have specific anticonvulsant activity in subhypnotic doses and are used in the treatment of epilepsy.

2. *Respiratory system* Barbiturates depress the respiration. High doses bring about a direct paralysis of the medullary respiratory centre and can be fatal.

3. *Cardiovascular system* Hypnotic doses of barbiturates produce a slight reduction in blood pressure and heart rate as seen during natural sleep.

Toxic doses of barbiturates produce a significant fall in BP due to direct decrease in myocardial contractility and vasomotor centre depression.

4. *Skeletal muscles* Higher doses of barbiturates depress the excitability of the neuromuscular junction.

Pharmacokinetics

Barbiturates are well-absorbed and widely distributed in the body. The highly lipid soluble barbiturates like thiopentone have a fast onset of action and duration is short due to redistribution into adipose tissues. Barbiturates are metabolised in the liver. They are hepatic microsomal enzyme inducers. The metabolites are excreted in urine.

Adverse Reactions

Hangover—due to residual depression of the CNS may be accompanied by nausea, vomiting, vertigo and diarrhoea. Distortions of mood, impaired judgement and fine motor skills may be evident. Barbiturates may cause excitement and irritability in some patients particularly children.

Barbiturates cause respiratory depression and in the presence of respiratory disorders even the hypnotic doses of barbiturates can cause serious respiratory depression. Hypersensitivity reactions like skin rashes, swelling of the eyelids and lips and rarely exfoliative dermatitis may be seen.

Barbiturates are contraindicated in porphyrias because they increase porphyrin synthesis.

Tolerance and dependence On repeated administration, tolerance develops to the effects of barbiturates.

Development of both psychological and physical dependence to barbiturates make them one of the drugs with abuse liability. Withdrawal symptoms include anxiety, restlessness, abdominal cramps, hallucinations, delirium and convulsions.

Acute barbiturate poisoning The fatal dose of phenobarbitone is 6-10 gm. Manifestations include respiratory depression with slow and shallow breathing, hypotension, skin eruptions, cardiovascular collapse and renal failure.

Treatment There is no specific antidote. The measures include:

1. Gastric lavage followed by administration of activated charcoal to prevent further absorption of barbiturates.
2. General supportive measures like maintenance of BP, patent airway, adequate ventilation and oxygen administration.
3. Forced alkaline diuresis with sodium bicarbonate, a diuretic and IV fluids will hasten the excretion of long-acting barbiturates through the kidneys since they are acidic drugs.
4. Haemodialysis should be done especially if there is renal failure.

Uses Because of respiratory depression and abuse liability, barbiturates are **generally not preferred**.

1. *Anaesthesia* Thiopentone sodium is used IV for the induction of general anaesthesia.

2. *Antiepileptic* Phenobarbitone is used as an antiepileptic (page 149).

3. *Neonatal jaundice* Phenobarbitone is a microsomal enzyme inducer and thereby enhances the production of glucuronyl transferase—the enzyme required for metabolism and excretion of bilirubin. It therefore helps in the clearance of jaundice in the neonates.

4. *Sedation and hypnosis* Benzodiazepines are preferred to barbiturates as sedative hypnotics.

5. *Peanesthetic medication* Barbiturates were used earlier for the sedative-hypnotic property, but are not preferred now.

MISCELLANEOUS

Chloral hydrate is used as an alternative to BZD. It has a bad taste and is an irritant—causes nausea and vomiting. It produces hypnosis without affecting respiratory and cardiovascular functions.

Meprobamate has sedative and antianxiety properties but is now not recommended. It produces respiratory depression, ataxia and is a drug of abuse.

Paraldehyde is a colourless, transparent, pungent, inflammable liquid. It is an irritant and can dissolve plastic—cannot be given by a plastic syringe. It is a good hypnotic causing little hangover. It can be given rectally, intramuscularly or orally.

It also has anticonvulsant properties.

Uses

1. As anticonvulsant in status epilepticus particularly in children; tetanus and eclampsia.
2. Hypnotic—rarely used.

ETHYL ALCOHOL (ETHANOL)

Ethyl alcohol is a monohydroxy alcohol manufactured by fermentation of sugars. It is a colourless, volatile, inflammable liquid. The ethanol content of various alcoholic beverages ranges from 4-55%.

Actions

1. *Local* On topical application, ethanol evaporates quickly and has a cooling effect. It is an astringent—precipitates surface proteins and hardens the skin. 40-50% alcohol is rubefacient and counter irritant. Alcohol is also an antiseptic. At 70%, it has maximum antiseptic properties which decrease above that. It is not effective against spores.

2. *CNS* Alcohol is a CNS depressant. Small doses cause euphoria, relief of anxiety and loss of social inhibitions. Moderate doses impair muscular coordination and visual acuity making driving dangerous. With higher doses mental clouding, impaired judgement, drowsiness and loss of self control result. High doses cause stupor and coma. Death is due to respiratory depression.

Alcohol may precipitate convulsions in epileptics. Tolerance develops on long-term use.

3. *CVS* The actions are dose dependent. Small doses cause cutaneous vasodilation resulting in flushing and feeling of warmth. Large doses cause hypotension due to

depression of myocardium and vasomotor centre.

4. *GIT and liver* Alcohol is an irritant—increases gastric secretion and produces vasodilation and warmth. It is an appetizer. Chronic alcoholism results in peptic ulcer.

Chronic consumption of moderate amounts of alcohol results in accumulation of fat in the liver, enlargement of the liver, followed by fatty degeneration and cirrhosis.

Alcohol induces microsomal enzymes.

5. *Other effects* Though alcohol is called an aphrodisiac, this effect could be due to loss of inhibition. Low doses taken over a long time increases HDL and lowers LDL cholesterol. Alcohol is a diuretic (↓ADH secretion). It interferes with folate metabolism and may cause megaloblastic anaemia. Though alcohol causes a feeling of warmth, heat loss is increased due to vasodilation and should not be used for 'warming up' in cold surroundings. Food value is 7 calories/gram.

Mechanism of Action

Ethanol acts by -

1. inhibiting central neuronal nicotinic acetylcholine receptors.
2. inhibiting excitatory NMDA (N-methyl-D-aspartate receptors mediate excitatory responses in the CNS and kainate receptor functions.

3. promoting the function of 5 HT₃ receptors.
4. ethanol also influences many ion channels including K⁺ channels.

Pharmacokinetics

Alcohol is rapidly absorbed from the stomach and is metabolised in the liver by alcohol and aldehyde dehydrogenase.

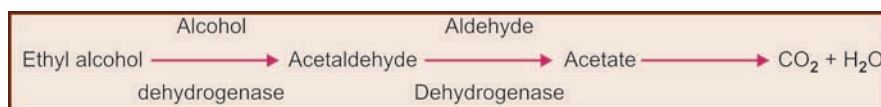
Metabolism follows zero order kinetics—a constant amount is metabolised per unit time, i.e. about 10 ml absolute alcohol is metabolised per hour. It is excreted through kidneys and lungs.

6. In methanol poisoning (See below)

Acute alcoholic intoxication causes severe gastritis, hypotension, hypoglycaemia, respiratory depression, coma and death.

Treatment measures include gastric lavage, airway maintenance, positive pressure ventilation and maintenance of fluid and electrolyte balance. Haemodialysis is needed in severe intoxication.

Chronic alcoholism causes dependence. Wernicke's encephalopathy, Korsakoff's psychosis, tremors, cirrhosis of liver, hypertension and cardiomyopathy can occur. In addition, nutritional deficiencies such as



Drug Interactions

1. Alcohol potentiates other CNS depressants including hypnotics, opioids and antipsychotics.
2. Sulfonylureas, metronidazole and griseofulvin have disulfiram like effects on alcohol consumption.
3. Alcohol is an enzyme inducer.

Uses

1. *Antiseptic*—70% alcohol is applied topically.
2. *Bedsore*s—When rubbed onto the skin, alcohol hardens the skin and prevents bedsores.
3. *Fever* Alcoholic sponges are used for reduction of body temperature in fevers.
4. *Appetite stimulant*—About 50 ml of 6-10% alcohol given before meals is an appetite stimulant.
5. *Neuralgias*—In severe neuralgias like trigeminal neuralgia, injection of alcohol around the nerve causes permanent loss of transmission and relieves pain.

polyneuritis, anaemia and pellagra can occur. In pregnant women, alcohol is teratogenic. Even moderate drinking during pregnancy can produce 'fetal alcohol syndrome' with manifestations like low IQ, microcephaly, growth retardation and facial anomalies in the foetus. It can also cause stillbirths and abortions.

Chronic alcoholics have poor dental hygiene resulting in a higher rate of associated dental ailments like periodontitis, gingivitis and dental plaque.

Treatment of alcohol dependence Disulfiram

Disulfiram inhibits the enzyme aldehyde dehydrogenase. If alcohol is consumed after taking disulfiram, acetaldehyde accumulates and within few minutes it can produce flushing, throbbing headache, nausea, vomiting, sweating, hypotension and confusion - called *the antabuse reaction*, due to accumulation of acetaldehyde. The effect lasts for 7-14 days after stopping disulfiram. The

reactions can sometimes be very severe and therefore treatment should be given in a hospital.

Other drugs that cause antabuse reaction are metronidazole, chlorpropamide, tolbutamide, griseofulvin, cephalosporins and phenylbutazone.

Contraindications Patients with liver disease, patients physically dependent on alcohol.

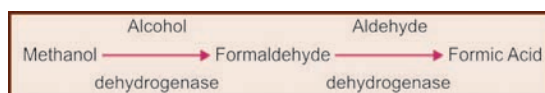
Other drugs—Several drugs are being tried in the pharmacotherapy of alcohol dependence. Orally effective opioid antagonists **naltrexone** and **nalmefene** reduce the urge and craving to drink and are recommended as adjuvants to other measures. They also reduce the chances of relapse of heavy drinking. **Ondansetron**, a 5HT₃ antagonist antiemetic has been shown to reduce alcohol consumption and is being evaluated for use in alcohol withdrawal. **Benzodiazepines** reduce the symptoms of alcohol withdrawal like anxiety and insomnia. **Clonidine** an α_2 agonist also reduces symptoms of sympathetic overactivity like tremors and tachycardia. **Acamprosate** an antagonist of NMDA receptor is also found to prevent relapse of heavy drinking.

METHYL ALCOHOL (METHANOL, WOOD ALCOHOL)

Methanol is used to denature ethyl alcohol. It is of no therapeutic value. Ingestion results in methanol poisoning. Methanol is converted to formaldehyde - catalysed by alcohol dehydrogenase; formaldehyde is converted to formic acid by the action of aldehyde dehydrogenase. Toxic effects are due to formic acid.

Manifestations of toxicity are vomiting, headache, vertigo, severe abdominal pain,

hypotension, delirium, acidosis and coma. Formic acid has affinity for optic nerve and causes retinal damage resulting in blindness. There are reports of even 15 ml of methanol causing blindness. Death is due to respiratory failure.



Treatment

1. **Correction of acidosis** As acidosis hastens retinal damage, immediate correction of acidosis with IV sodium bicarbonate infusion helps in preventing blindness.
2. **Protect eyes** Patient should be kept in a dark room to protect the eyes.
3. **Gastric lavage** should be given.
4. **BP and ventilation** should be maintained.
5. **Ethyl alcohol** should be given immediately. It competes with methanol for alcohol dehydrogenase, because of its higher affinity for alcohol dehydrogenase. It thus slows the metabolism of methanol and prevents the formation of toxic metabolites. A loading dose of 0.6 g/Kg is followed by an infusion of 10 g/hour.
6. **Antidote** Fomepizole specifically inhibits the enzyme alcohol dehydrogenase and thereby prevents the formation of toxic metabolites—formaldehyde and formic acid. Fomepizole thus acts as an antidote in methanol poisoning. It has an advantage over ethyl alcohol that it does not cause any intoxication by itself.
7. **Haemodialysis** should be started at the earliest possible.

Antiepileptics

Epilepsy is a common neurological abnormality that affects about 0.5-1% of the population. Epilepsy is a chronic disorder characterised by recurrent seizures often accompanied by episodes of unconsciousness and/or amnesia. It is a disorder of brain function.

Seizure indicates a transient alteration in behaviour because of disordered firing of groups of brain neurons. Such discharges may spread to other parts of the brain to different extents. In most of the cases, the cause is not known. It may be due to various reasons including trauma during birth process, head injury, childhood fevers, brain tumours, meningitis or drug induced.

Seizures have been classified into partial and generalised seizures.

Partial seizures account for about 60% of all epilepsies and begin focally in the cortex, i.e. they involve focal brain regions. It is classified as simple partial in which there is no impairment of consciousness and complex partial seizures with impairment of consciousness. When reticular formation is affected unconsciousness results.

Simple partial seizures There is no impairment of consciousness. The manifestation depends on the site in the cortex that is activated by the seizure, e.g. if the motor cortex representing the right thumb is involved, there is recurrent contractions of the right

thumb. If the sensory area representing the left palm is involved, there is numbness or paraesthesia of the left palm. This type of seizures lasts for 20-60 seconds.

Complex partial seizures are the most common types of epilepsy. They are characterised by purposeless movements like lipsmaking, hand wringing or swallowing that lasts for 30 sec to 2 minutes. Consciousness is impaired and may be preceded by an *aura*.

Partial with secondarily generalised seizures Simple or complex partial seizure may evolve into a generalised seizure.

Generalised seizures Account for 40% of all epilepsies and is usually of genetic aetiology. Generalised seizures affect the whole brain. They may be:

Absence seizures (petit mal) In this, there is a sudden onset of impaired consciousness associated with staring. The person stops all on-going activities and the episode lasts for a brief period usually less than 30 sec.

Myoclonic seizures involve a sudden, brief, shock like contraction of muscles. It may be limited to a part of the body or may affect the whole body.

Atonic seizures (Drop attacks) are characterised by sudden loss of postural tone and the head may drop for a few seconds or the person may drop to the ground for no obvious reasons.

Tonic-clonic seizures (Grand mal epilepsy) is characterised by sudden loss of consciousness

followed by sustained contraction of muscles throughout the body (known as tonic phase), lasting for 1 minute and then, a series of jerks, i.e. periods of muscle contraction alternating with periods of relaxation (clonic phase) lasting for 2-4 minutes follow. CNS depression then occurs and the person goes into sleep. Injury may occur during the convulsive episode.

Status epilepticus is continuous or recurrent seizures of any variety without recovery of consciousness between the attacks.

Mechanism of Action of Antiepileptics

Antiepileptics act by one or more of the following mechanisms (Fig. 24.1):

- Blockade of Na^+ channels and prolongation of their inactive state delaying their recovery, e.g. phenytoin, carbamazepine, lamotrigine.
- Blockade of low threshold Ca^{++} current (T-type) in the thalamic neurons - controls absence seizures, e.g. ethosuximide.
- Enhancing GABA mediated inhibition
 - by acting on GABA receptors, e.g. benzodiazepines

- by inhibiting GABA metabolism, e.g. valproic acid, vigabatrin.
- by blocking excitatory glutamate receptors, e.g. topiramate and some drugs under investigation.

CLASSIFICATION

<i>Hydantoins</i>	Phenytoin, mephenytoin
<i>Barbiturates</i>	Phenobarbitone, mephobarbitone
<i>Deoxybarbiturate</i>	Primidone
<i>Iminostilbene</i>	Carbamazepine
<i>Succinimide</i>	Ethosuximide
GABA transaminase inhibitors	Valproic acid, vigabatrin
<i>Benzodiazepines</i>	Diazepam, clonazepam, lorazepam, clorazepate
Newer agents	
GABA analogues	Gabapentin, vigabatrin, tiagabine.
Others	Lamotrigine, levetiracetam, felbamate, topiramate, zonisamide.

Phenytoin (Diphenylhydantoin) was synthesized in 1908, but its anticonvulsant property was discovered only in 1938.

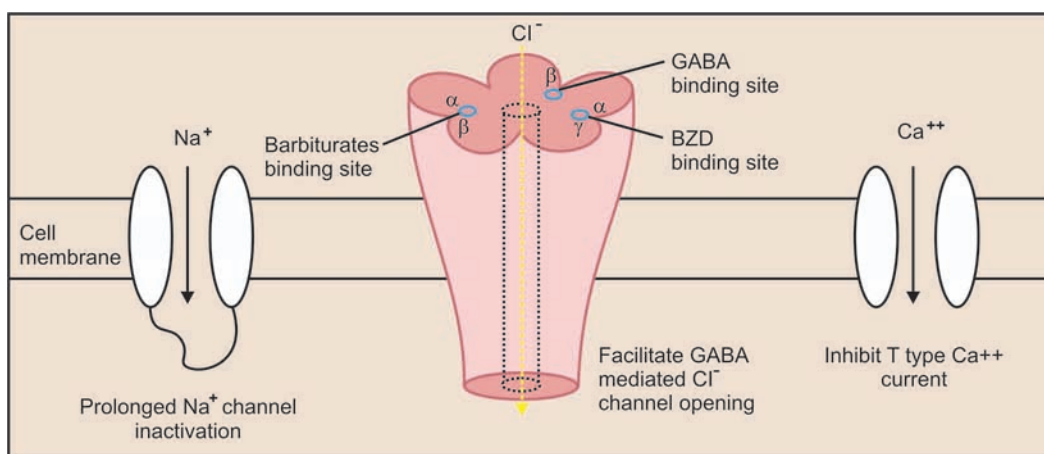


Fig 24.1: Mechanisms of action of antiepileptics. Antiepileptics may act by blockade of Na^+ channels, by facilitating GABA activity or by blockade of Ca^{++} current.

Pharmacological Actions

CNS Phenytoin has good antiseizure activity and is one of the most effective drugs against generalised tonic-clonic seizures and partial seizures. It brings about its effects without causing general depression of the CNS.

Mechanism of Action

Phenytoin causes blockade of the voltage dependent sodium channels and stabilizes the neuronal membrane. It inhibits the generation of repetitive action potentials.

Voltage dependent Na^+ channels enter an inactive stage after each action potential. Phenytoin blocks the Na^+ channels which are in an inactivated state and delay the recovery of these channels from inactivation. It decreases the number of channels which are available for the generation of action potentials and it inhibits the membrane excitability of these voltage-dependent Na^+ channels. Phenytoin preferentially blocks high frequency firing (neurons in normal state have low frequency firing while in seizures, high-frequency firing occurs).

Pharmacokinetics

Phenytoin is poorly water-soluble—hence absorption is slow. Phenytoin is 90% bound to plasma proteins. Valproic acid competes with phenytoin for plasma protein binding sites and may result in phenytoin toxicity. It is metabolised in the liver initially by first order and later by zero order kinetics as the dose increases. Therefore monitoring of plasma concentration is useful. Phenytoin is an enzyme inducer. Dose table 24.1.

Adverse Effects

Adverse effects depend on the dose, duration and route of administration.

1. Nausea, vomiting, epigastric pain, anorexia.

2. Nystagmus, diplopia, ataxia are common.
 3. Gingival hyperplasia—Long-term administration of phenytoin can result in gingival hyperplasia particularly in children with poor oral hygiene. Maintaining good oral hygiene can prevent this. However, it is generally reversible though it takes 1-2 years after the discontinuation of phenytoin.
 4. Peripheral neuropathy.
 5. Endocrine
 - i. Hirsutism, acne, coarsening of facial features.
 - ii. Hyperglycaemia – as phenytoin inhibits insulin release.
 - iii. ↓ release of ADH.
 - iv. Osteomalacia, hypocalcaemia due to altered metabolism of vitamin D and inhibition of intestinal absorption of Ca^{++} . Phenytoin also reduces target tissue sensitivity to vitamin D.
 6. Hypersensitivity—rashes, hepatic necrosis, lymphadenopathy and neutropenia. Idiosyncratic reactions including hepatic necrosis and systemic lupus erythematosus, have been reported.
 7. Megaloblastic anaemia—because phenytoin decreases absorption and increases excretion of folates.
 8. Teratogenicity—when taken by the pregnant lady, phenytoin produces *foetal hydantoin syndrome* characterised by hypoplastic phalanges, cleft palate, harelip and microcephaly in the offspring.
- Toxic doses—cerebellar and vestibular effects are prominent; drowsiness, delirium, confusion, hallucinations, altered behaviour and coma follow.

Uses

1. Generalised tonic-clonic seizures and partial seizures (not useful in absence seizures).

2. Status epilepticus–phenytoin is used by slow IV injection.
3. Trigeminal neuralgia—as an alternative to carbamazepine.
4. Cardiac arrhythmias–Phenytoin is useful in digitalis induced arrhythmias (see page 101).

Drug Interactions

- Phenytoin is an enzyme inducer. Given with phenobarbitone, both increase each other's metabolism. Also phenobarbitone competitively inhibits phenytoin metabolism.
- Carbamazepine and phenytoin enhance each other's metabolism.
- Valproate displaces protein bound phenytoin and may result in phenytoin toxicity.
- Cimetidine and chloramphenicol inhibit the metabolism of phenytoin resulting in toxicity.
- Antacids ↓ absorption of phenytoin. Mephenytoin, ethatoin and phenacemide are congeners of phenytoin. Ethatoin can be used as an alternative in patients allergic to phenytoin. Adverse effects of ethatoin are milder. Phenacemide is used in patients with refractory partial seizures when other drugs fail. It is a highly toxic drug.

PHENOBARBITONE (See Chap 22)

Phenobarbitone was the first effective antiepileptic drug to be introduced in 1912. It still remains one of the widely used drugs. *Antiepileptic actions* Phenobarbitone has specific antiepileptic activity and raises the seizure threshold. Primidone which is rarely used now is metabolised to phenobarbitone. Phenobarbitone is effective in tonic-clonic seizures and is ineffective in absence seizures. Though other barbiturates also have

PHENYTOIN

- Blocks voltage dependent Na^+ channels.
- Preferably blocks high frequency firing that is seen in seizures.
- Blocks Na^+ channels in an inactivated state and delays their recovery.
- Main adverse effects include vestibular effects, G.I. disturbances; long term use results in gum hyperplasia, hirsutism and megaloblastic anaemia.
- It is teratogenic.
- Used in partial and generalised tonic-clonic seizures.

anticonvulsant effects, the dose required produces significant sedation.

Mechanism of action Barbiturates enhance the inhibitory neurotransmission in the CNS by enhancing the activation of GABA_A receptors and thus facilitating the GABA -mediated opening of chloride ion channels.

Pharmacokinetics Oral absorption of phenobarbitone is slow but complete. About 50% is bound to plasma proteins. It is a microsomal enzyme inducer and can result in many drug interactions.

Adverse effects Sedation is the most common side effect. Tolerance develops to some extent to sedation after prolonged use. Phenobarbitone can also cause nystagmus, ataxia, megaloblastic anaemia and osteomalacia like phenytoin. Skin rashes and other hypersensitivity reactions can occur.

Uses Phenobarbitone is still widely used because of its efficacy and low cost. However, carbamazepine and phenytoin are often preferred. Phenobarbitone can be used in:

1. Generalised tonic-clonic seizures.
2. Partial seizures.

CARBAMAZEPINE

Carbamazepine is a tricyclic compound closely related to imipramine. It is one of the most commonly used antiepileptic drugs.

Antiseizure activity Carbamazepine has good anti-seizure activity. Its mechanism of action and antiepileptic actions are similar to phenytoin, i.e. it blocks sodium channels.

Carbamazepine is also useful in the treatment of trigeminal neuralgia (severe pain along the distribution of the trigeminal nerve) and glossopharyngeal neuralgia. It is also found to be beneficial in mood disorders. Carbamazepine has mild antidiuretic effects. **Pharmacokinetics** Absorption is slow and erratic; has a $t_{1/2}$ of 10-30 hours. Carbamazepine is a powerful microsomal enzyme inducer. Therefore, after repeated administration, its $t_{1/2}$ reduces to 15 hours due to autoinduction.

Adverse effects Drowsiness, vertigo, ataxia, diplopia, blurring of vision, nausea, vomiting and dizziness are common. Driving is therefore dangerous for patients on carbamazepine. It also causes water retention due to antidiuretic effects. Hypersensitivity reactions—like skin rashes may occur. Haematological toxicity includes leukopenia, thrombocytopenia and rarely agranulocytosis and aplastic anaemia. It is a teratogen. Its $t_{1/2}$ reduces to 15 hrs due to autoinduction.

Uses

1. Generalised tonic-clonic seizures (grand mal epilepsy).
2. Simple and complex partial seizures—especially temporal lobe epilepsy.
3. Trigeminal neuralgia and glossopharyngeal neuralgia—carbamazepine is the drug of choice for these neuralgias and has to be given for several months.
4. Carbamazepine is also found to be useful in chronic neuropathic pain and in tabetic pain.
5. Bipolar mood disorder—carbamazepine is used as an alternative to lithium as a mood stabilizer (see Page 200).

Oxcarbazepine—is similar to carbamazepine in action and uses. It has the following

advantages over carbamazepine - fewer hypersensitivity reactions, milder induction of microsomal enzymes - hence fewer drug interactions. It has been tried as an alternative to carbamazepine in partial seizures.

ETHOSUXIMIDE

Ethosuximide is a succinimide. It raises the seizure threshold.

Mechanism of action Ethosuximide reduces the low threshold calcium currents (T-currents) in the thalamic neurons. These T currents are thought to be responsible for absence seizures.

Pharmacokinetics Absorption is complete on administration of oral dosage forms. It is metabolised in the liver.

Adverse effects The most common adverse effects are nausea, vomiting, epigastric pain, gastric irritation and anorexia. These can be avoided by starting with a low dose and gradually increasing it. CNS effects like drowsiness, fatigue, lethargy, euphoria, dizziness, headache and hiccough are dose-related effects. Hypersensitivity reactions like rashes, urticaria, leukopenia, thrombocytopenia or pancytopenia have been reported.

Uses Ethosuximide is the drug of choice for absence seizures.

VALPROIC ACID

Valproic acid (salt→sodium valproate) is a very effective antiepileptic drug useful in many types of epilepsies including absence seizures, partial and generalised tonic-clonic seizures.

Divalproex sodium is a combination of valproic acid and sodium valproate. The combination is said to have a better bioavailability and is better tolerated.

Mechanism of action Valproic acid acts by multiple mechanisms.

1. It enhances the level of GABA by:
 - i. increasing the synthesis of GABA—by increased activity of GABA synthetase enzyme.
 - ii. decreasing the metabolism of GABA—by inhibiting GABA transaminase enzyme.
2. Like phenytoin, valproic acid blocks the sodium channels.
3. Like ethosuximide valproate decreases low threshold Ca^{++} (T-currents) current in the thalamus.

Adverse effects Gastrointestinal symptoms like nausea, vomiting, epigastric distress occur initially. Tremors, sedation, ataxia, rashes and alopecia are rare. An idiosyncratic response causing fulminant hepatitis—though rare can be fatal. Hence careful monitoring of liver functions is mandatory. Valproic acid is teratogenic, it can cause neural tube defects including spina bifida.

Uses Useful in partial and generalised seizures. Valproic acid is particularly useful

in absence seizures. In patients with both absence seizures and generalised tonic-clonic attacks, valproate is the drug of choice.

Valproate is also useful as a mood stabilizer in bipolar mood disorder.

BENZODIAZEPINES

Benzodiazepines have useful anticonvulsant properties. *Diazepam* is the drug of choice in status epilepticus. *Clonazepam* is a potent antiepileptic useful in absence and myoclonic seizures. But tolerance develops to its antiepileptic effects. *Clobazam* causes less sedation and is effective in most types of epilepsies—used as an adjuvant to other antiepileptic drugs.

NEWER ANTIEPILEPTICS (Table 24.1)

Gabapentin is a highly lipid soluble analogue of GABA which was designed to cross the BBB. It is effective in tonic-clonic seizures. Its exact mechanism of action is not known, but it does not act on GABA receptors.

Table 24.1: Therapeutic dose of antiepileptic drugs

Drug	Dose	Trade name
Phenytoin	100 mg BD Children 5-8 mg/kg/day	EPILEPTIN EPTOIN
Carbamazepine	200-400 mg TDS Children 15-30 mg/kg/day	TEGRETOL, CARBATOL
Phenobarbitone	60 mg OD - TDS Children 3-6 mg/kg/day	GARDINAL
Ethosuximide	20-30 mg/kg/day	ZARONTIN
Valproic acid	200-500 mg TDS Children 15-30 mg/kg/day	VALPARIN
Clonazepam	0.5 - 5 mg TDS Children 0.01 - 0.2 mg/kg/day	CLONOTRIL
Clobazam	10-20 mg HS Max 60 mg HS	FRISIUM
Lamotrigine	50-300 mg/day	LAMITOR
Gabapentin	300 mg OD - TDS	NEURONTIN

Newer antiepileptics:

- Gabapentin, vigabatrin, tiagabine, lamotrigine, levetiracetam, topiramate, felbamate, zonisamide.
- All are generally well tolerated except that felbamate can rarely cause aplastic anaemia and hepatitis.
- Presently they are recommended as add-on drugs in refractory partial seizures.

Advantages Absorption of gabapentin depends on a carrier protein and does not increase with increase in dose - hence it is safe. It is well tolerated. It does not influence the plasma concentrations of other antiepileptics.

Adverse effects include ataxia, fatigue, drowsiness and dizziness. Tolerance develops to these effects in 1-2 weeks.

Gabapentin is used in combination with other antiepileptic drugs, as an add-on drug in partial seizures. It is also used in migraine, neuropathic pain and in bipolar mood disorder.

Progabalin is a prodrug, which is more potent than gabapentin.

Lamotrigine has a broad spectrum of antiepileptic activity. It inhibits the sodium channels and also inhibits the release of the excitatory amino acids like glutamate. It is completely absorbed from the gut. Lamotrigine may cause skin rashes, nausea, ataxia and dizziness. It is used either alone or with other drugs in partial and generalized seizures.

Vigabatrin is a GABA analogue which acts by irreversibly inhibiting the enzyme GABA transaminase thereby raising brain GABA levels. It can cause depression in some patients. Vigabatrin is useful in patients not responding to other antiepileptics.

Levetiracetam is effective against partial and secondarily generalized seizures. Its mechanism of action is not known. It is not an enzyme inducer-no related drug interactions. Levetiracetam can be used as an add-on drug in refractory partial seizures.

Tiagabine a GABA analogue, inhibits the reuptake of GABA into neurons and thereby enhances extracellular GABA levels. It may cause drowsiness and dizziness. Tiagabine can be used as an add-on drug for refractory partial seizures.

Topiramate a monosaccharide, acts by multiple mechanisms. It blocks the sodium channels, enhances GABA_A receptor currents, blocks AMPA receptors (glutamate receptor). It is effective in partial and generalized seizures. Topiramate can be used as add-on therapy in refractory epilepsy.

Felbamate an analogue of meprobamate is found to have good antiepileptic action. It blocks the NMDA receptors in addition to weak sodium channel blocking effect. But felbamate can sometimes cause serious adverse effects like aplastic anaemia and hepatitis because of which it is employed only in refractory epilepsy.

Zonisamide a sulfonamide derivative acts by inhibiting T type Ca⁺⁺ currents and also by blocking Na⁺ channels. It is well tolerated and is indicated in refractory partial seizures.

TREATMENT OF EPILEPSIES

An attempt should be made to detect the cause. When drugs are found to be necessary, the goal of therapy is to keep the patient free of seizures (Table 24.2) without interfering with normal daily activity. Treatment should be started with a single drug at a low dose; dosage is increased gradually, preferably by monitoring the drug levels in plasma.

Table 24.2: Choice of antiseizure drugs

<i>Types of seizures</i>	<i>Preferred drugs</i>
1. Simple partial seizures	Carbamazepine, Phenytoin Valproic acid
2. Complex partial seizures	Carbamazepine, Phenytoin, Valproic acid
3. Partial with secondarily generalised tonic-clonic seizures	Carbamazepine, Phenytoin, Valproic acid
4. Absence seizures	Ethosuximide, Valproate
5. Tonic-clonic seizures	Carbamazepine, Phenytoin Valproic acid
6. Tonic-clonic + absence seizures	Valproic acid
7. Myoclonic seizures	Diazepam, Valproic acid
8. Status epilepticus	Diazepam, Phenytoin, General anaesthesia
9. Febrile convulsions	Diazepam

Good compliance is very important for success. Regarding the duration—decision should be made on an individual basis and dose should be very gradually reduced over months to avoid status epilepticus.

Febrile convulsions Two to four per cent of children experience convulsions during fever; of them 2-3% become epileptics. Treatment is controversial. Children <18 months developing febrile convulsions, those with neurological abnormalities and those with seizures lasting for > 15 minutes, complex seizures—all these have greater risk of recurrence. Diazepam (0.5 mg/kg) given orally or rectally at the onset of fever prevents convulsions. Timely use of paracetamol and tepid sponging prevent high fever. If convulsions occur, diazepam (rectally or intravenously) can be used.

Status epilepticus is a neurological emergency which may be fatal. Diazepam IV 5-10 mg every 10-15 minutes up to 30 mg is the drug

of choice or phenytoin IV can be given. A loading dose 500-1000 mg phenytoin (max 1000 mg in 24 hr) takes 15-20 min to act. Some prefer to combine diazepam and phenytoin (60 mg/min). If seizures continue-general anaesthesia is the last resort. Airway maintenance is important. After the control of seizures, long-term antiepileptic therapy is needed.

In pregnancy—antiepileptics should be continued because abrupt discontinuation increases the risk of status epilepticus which is hazardous to the foetus.

Epilepsy and Dentistry

1. When patients on antiepileptics are admitted for dental procedures, antiepileptic drugs should be continued and not stopped.
2. Long-term administration of phenytoin can induce gingival hyperplasia. This is

more common in children with poor oral hygiene. It is thought to be an exaggerated drug induced response of gingival tissues to the oral plaque.

3. Though uncommon, some patients might have convulsions while undergoing a dental procedure (See page 400). The procedure should be immediately stopped. All instruments and dentures should be removed from the oral cavity. Gentle passive restraints should be used to prevent physical injury. A padded tongue depressor should be placed in the mouth to protect the tongue from getting bitten. The head should be turned to a side so that the tongue does not obstruct the airway. If the convulsions continue, diazepam 10 mg may be given intravenously over 1-2 minutes. Physicians' help should be sought at the earliest possible.
4. Long-term administration of some antiepileptics like sodium valproate can increase the bleeding tendency. Appropriate precautions should be taken to control bleeding during dental procedures.

Drugs Used in Parkinsonism

Parkinsonism is a chronic, progressive, motor disorder characterised by rigidity, tremors and bradykinesia. Other symptoms include excessive salivation, abnormalities of posture and gait, seborrhoea and mood changes. It was described by James Parkinson in 1817 and is therefore named after him.

The incidence is about 1 per cent of population above 65 years of age. It is usually idiopathic in origin but can also be drug induced. In idiopathic parkinsonism, there is degeneration of nigrostriatal neurons in the basal ganglia resulting in dopamine deficiency. The balance between inhibitory dopaminergic neurons and excitatory cholinergic neurons is disturbed.

Antiparkinsonian drugs can only help to alleviate the symptoms and improve the quality of life. The two strategies in the treatment are-

- (i) to enhance dopamine activity
- (ii) to depress cholinergic overactivity.

Often combination of drugs are used to influence both functions.

CLASSIFICATION

Drugs used in parkinsonism can be classified as -

1. **Drugs that increase dopamine levels**
 - i. *DA precursor*
Levodopa
 - ii. *Drugs that release dopamine*
Amantadine

- iii. *Dopaminergic agonists*

- Bromocryptine
- Lisuride
- Ropinirole
- Pramipexole

- iv. *Inhibit dopamine metabolism*

- MAO inhibitors
Selegiline
- COMT inhibitors
Tolcapone
Entacapone

2. *Drugs influencing cholinergic system*

- i. *Central anticholinergics*

- Benztropine
- Benzhexol
- Biperidine
- Trihexyphenidyl

- ii. *Antihistamines*

- Diphenhydramine
- Orphenadrine
- Promethazine

DOPAMINE PRECURSOR

Levodopa

Though parkinsonism is due to dopamine deficiency, dopamine is of no therapeutic value because it does not cross the blood-brain barrier. Levodopa is a prodrug which is converted to dopamine in the body. It crosses the BBB and is taken up by the surviving nigrostriatal neurons.

*Dopa
decarboxylase*

Levodopa —————→ Dopamine

Antiparkinsonian effect On administration of levodopa, there is an overall improvement in the patient as all the symptoms subside.

Other actions Large amounts of levodopa are converted to dopamine in the periphery which brings about other actions.

- **CTZ**—Dopamine stimulates the CTZ to induce vomiting.
- **CVS**— It causes postural hypotension, tachycardia and arrhythmias. Dopamine is a catecholamine.
- **Endocrine**—Dopamine suppresses the prolactin secretion.

Pharmacokinetics

Levodopa is rapidly absorbed from the small intestine. Presence of food delays absorption. Some amino acids in the food compete with levodopa for absorption and transport to the brain. It undergoes first pass metabolism in the gut and the liver. Its $t_{1/2}$ is 1-2 hours.

Adverse Reactions

As 95% of levodopa is converted to dopamine in the periphery, several adverse effects are expected. Nausea, vomiting, anorexia, postural hypotension, palpitation and occasionally arrhythmias can occur. Tolerance develops to these effects after some time. These peripheral effects can be prevented by concurrent administration of domperidone which is a peripheral dopamine antagonist. Behavioural effects like anxiety, depression, hallucinations and sometimes psychosis can occur.

Abnormal involuntary movements like facial tics, grimacing, choreoathetoid movements of the limbs may develop after a few months of use and require reduction in the dose of levodopa.

Fluctuation in response to levodopa can occur after 2-5 years of use—known as ‘on-off’ phenomenon—where the patient swings alternately from periods of good response to severe disabling disease.

Uses Levodopa is the most effective drug in idiopathic parkinsonism but is not useful in drug induced parkinsonism.

Drug interactions

1. Pyridoxine enhances peripheral decarboxylation of levodopa and thus reduces its availability to the CNS.
2. Phenothiazines and metoclopramide are DA antagonists. They reverse the effects of levodopa.

Carbidopa and Benserazide

Carbidopa and benserazide are peripheral dopa decarboxylase inhibitors. When carbidopa or benserazide are given with levodopa, they prevent the formation of dopamine in the periphery. They do not cross the BBB and hence allow levodopa to reach the CNS. The combination is synergistic and therefore levodopa is always given with carbidopa/benserazide.

Advantages of the combination

1. Dose of L-dopa can be reduced by 75%.
2. Response to L-dopa appears earlier.
3. Side effects like vomiting and tachycardia are largely reduced.
4. Pyridoxine does not interfere with treatment.

DRUGS THAT RELEASE DOPAMINE

Amantadine is an antiviral drug. It enhances the release of DA in the brain and diminishes the re-uptake of DA. The response starts early and its adverse effects are minor. Large doses produce insomnia, dizziness, vomiting, postural hypotension, hallucinations and ankle oedema.

Amantadine is used in mild cases of parkinsonism. It can also be used along with levodopa as an adjunct.

DOPAMINE RECEPTOR AGONISTS

Bromocriptine and *pergolide* are ergot derivatives having dopamine agonistic activity at D₂ receptors. Bromocriptine is also a partial agonist while pergolide is an agonist at D₁ receptors. The newer agents ropinirole and pramipexole are selective D₂ agonists, are better tolerated, quickly attain therapeutic levels and adverse effects are milder except that they may cause some sleep disorders.

Dopamine agonists are all longer acting because of which they are useful in the treatment of 'on-off' phenomenon.

Adverse effects include nausea, vomiting, hallucinations and skin eruptions. Ergot derivatives can cause postural hypotension or hypertension initially and first dose phenomenon—sudden cardiovascular collapse.

DA agonists are used:

1. in the treatment of 'on-off' phenomenon
2. as alternatives in the initial treatment of parkinsonism (particularly newer agents).

Lisuride is similar to bromocriptine.

DRUGS THAT INHIBIT DA METABOLISM

MAO Inhibitor

Selegiline (Deprenyl) is a selective MAO-B inhibitor. MAO-B is present in DA containing regions of the CNS. Selegiline prolongs the action of levodopa by preventing its degradation. Selegiline may delay the progression of parkinsonism.

Adverse effects include nausea, postural hypotension, confusion and hallucinations.

Uses Mild cases of parkinsonism are started on selegiline. It is also used as an adjunct to levodopa.

COMT Inhibitors

Tolcapone and *entacapone* inhibit the peripheral metabolism of levodopa thereby increasing its bioavailability. Tolcapone crosses the BBB and enhances the availability of levodopa in the brain.

Adverse effects are nausea, orthostatic hypotension, confusion and hallucinations. Tolcapone can also cause hepatotoxicity.

COMT inhibitors are used as add-on drugs in parkinsonism.

ANTICHOLINERGICS

The cholinergic overactivity is overcome by anticholinergics. Tremors, seborrhoea and sialorrhoea are reduced more than rigidity. Atropine derivatives like benzhexol, benztropine, trihexyphenidyl are used. Antihistamines owe their beneficial effects in parkinsonism to their anticholinergic properties. Atropine-like side effects such as dry mouth, constipation, urinary retention and blurred vision may be encountered.

Uses Anticholinergics are used as (i) adjunct to levodopa, (ii) drugs of choice in drug-induced parkinsonism.

Drug induced parkinsonism Drugs like reserpine, metoclopramide and phenothiazines can induce parkinsonism. Reserpine depletes catecholamine stores, while metoclopramide and phenothiazines are dopamine antagonists.

Treatment Withdrawal of the drug usually reverses the symptoms. When drugs are needed, one of the anticholinergics are effective. Levodopa or other dopamine agonists are *not effective* because DA receptors are blocked by drugs like metoclopramide and phenothiazines.

Opioid Analgesics

Pain or algesia is an unpleasant subjective sensation. It cannot be easily defined. Pain is a warning signal and indicates that there is an impairment of structural and functional integrity of the body. It is the most important symptom that brings the patient to the doctor and demands immediate relief. Prompt relief of pain instills enormous confidence in the patient regarding the doctor's treating ability.

Pain arising from the skin and integumental structures, muscles, bones and joints is known as *somatic pain*. It is usually caused by inflammation and is well-defined or sharp pain.

Pain arising from the viscera is vague, dull-aching type, difficult to pinpoint to a site and is known as *visceral pain*. It may be accompanied by autonomic responses like sweating, nausea and hypotension. It may be due to spasm, ischaemia or inflammation.

When pain is referred to a cutaneous area which receives nerve supply from the same spinal segment as that of the affected viscera, it is known as *referred pain*, e.g. cardiac pain referred to the left arm.

Pain consists of 2 components - the original 'sensation' and the 'reaction' to it. The original sensation is carried by the afferent nerve fibres and is the same in all. The reaction component differs widely from one person to another. Perception of pain is increased in

presence of anxiety. A person who is already in stress can poorly tolerate pain.

Pain may be acute or chronic. Acute pain may result from wounds, irritants, burns or from ischaemia. The cause is usually well defined. In chronic pain the origin may not be well defined. Example: Pain due to arthritis, cancers and neuropathic pain.

Analgesic

Analgesic is a drug which relieves pain without loss of consciousness. Analgesics only afford symptomatic relief from pain without affecting the cause.

Analgesics are of 2 classes.

- Opioid or morphine type of analgesics
- Non-opioid or aspirin type of analgesics.

OPIOID ANALGESICS

Opioid analgesics are one of the oldest remedies for relief of pain.

Opium is the dark brown gummy exudate obtained from the poppy capsule (*Papaver somniferum*). On incising the unripe seed capsule, a milky juice emerges which turns brown on drying and this is crude opium. The word opium is derived from Greek in which '*opos*' means juice. Opium has been in use since 4000 BC. It was used both for medicinal and recreational purposes. By 18th century, opium smoking had become quite

popular in Europe. It was Serturmer who isolated a pure opium alkaloid in 1806. He named it *Morphine* after Morpheus, the Greek God of dreams. As the research progressed, opium was found to contain 20 alkaloids. By around 19th century, the pure opium alkaloids were available for therapeutic use - but because they were equally abused, efforts were made to isolate their analgesic property, i.e. to obtain an opioid that is only an analgesic and has no euphoric effects. In the process, various agonists, antagonists and partial agonists were synthesized. 'Opioid' is the term used for drugs with morphine-like actions. They were earlier called narcotic analgesics.

CLASSIFICATION

Based on receptor occupation

1. *Agonists*
 - Natural opium alkaloids
Morphine, codeine
 - Synthetic opioids
Pethidine, methadone
2. *Antagonists*
Naloxone, naltrexone
3. *Mixed agonist-antagonists*
Pentazocine, nalbuphine, butorphanol, buprenorphine, nalorphine

Chemically the opium alkaloids can be grouped into:

1. *The Phenanthrene group*
Morphine, codeine, thebaine
2. *The Benzylisoquinoline group*
Papaverine, noscapine, narcine.

Opioids can also be classified depending on their source as

1. *Natural opium alkaloids*
Morphine, codeine, noscapine
2. *Semisynthetic derivatives*
Heroin, oxymorphone, pholcodeine
3. *Synthetic opioids*
Pethidine, fentanyl, diphenoxylate, loperamide, dextropropoxyphene, methadone, tramadol, ethoheptazine.

Morphine

Morphine is the most important alkaloid of opium. Many new opioids with actions similar to morphine have been synthesized. But none of them are superior to morphine as an analgesic. Morphine is discussed as the prototype of the group.

Mechanism of Action

Morphine and other opioids produce their effects by acting on specific opioid receptors. (Fig. 26.1) These receptors are abundant in the CNS and other tissues. The opioid receptors are *mu* (μ), *kappa* (κ) and *delta* (δ). It is found that there are 3 families of endogenous opioid peptides released in the body in response to pain *viz* the *enkephalins*, the *endorphins* and the *dynorphins*. This indicates that we have a natural system in the body that releases various opioid peptides in response to pain. These opioid peptides act on opioid receptors and relieve pain. Most pharmacological effects of opioids including analgesia, sedation, euphoria, respiratory depression, miosis and constipation are mediated through μ receptors. 'Endomorphins' are endogenous ligands for μ receptors but other endogenous peptides also bind to μ receptors. Dynorphins are endogenous ligands for κ receptors while enkephalins bind δ receptors. Various subtypes of these receptors are now known. A fourth type of opioid receptor was recently identified. It is called nociceptin (N) / orphanin FQ receptor.

All opioid receptors are G-protein-coupled receptors. Stimulation of these receptors inhibits adenylyl cyclase resulting in decreased intracellular cAMP formation. They also facilitate the opening of K^+ channels leading to hyperpolarisation and inhibit the entry of calcium into the cell. In addition to this they inhibit the opening of calcium

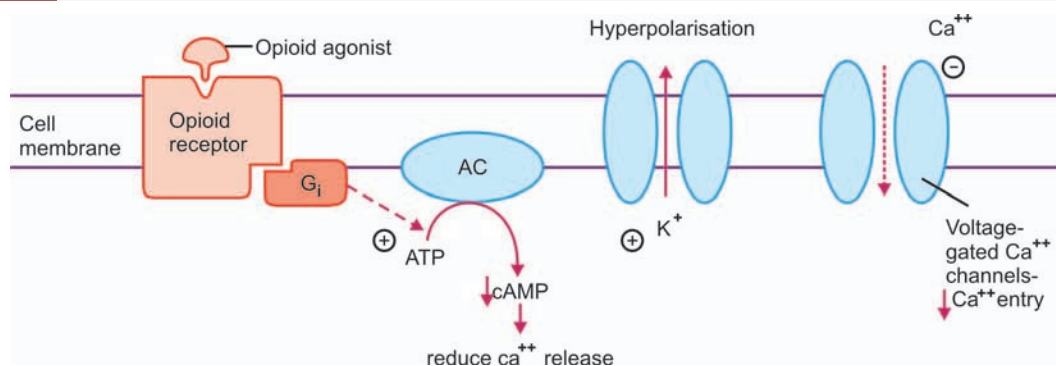


Fig . 26.1: Mechanisms of action of opioids. Opioid receptors are G-Protein coupled receptors. Stimulation of these receptors $\downarrow$ cAMP formation, $\uparrow$ K^+ efflux causing hyperpolarisation and also inhibit Ca^{++} entry through voltage gated Ca^{++} channels. AC=Adenylyl cyclase cAMP=cyclic AMP.

channels. All these result in a decrease in the intracellular calcium which, in turn, decrease the release of neurotransmitters. Various neurotransmitters including dopamine, glutamate, GABA, NA, 5HT and substance P are involved in transmission of pain impulses.

Opioids also directly inhibit the transmission in the dorsal horn ascending pathway. Opioids stimulate the descending pain control pathway - from the midbrain and brainstem to the dorsal horn of the spinal cord. Opioid receptors are abundant in these areas including the peri-aqueductal grey (PAG) area, substantia gelatinosa and the spinal cord.

Pharmacological Actions

Central Nervous System

1. **Analgesia** Morphine is a potent analgesic and relieves pain without loss of consciousness. Dull aching visceral pain is relieved better than sharp pricking pain (Table 26.1). But in higher doses it relieves even the severe pain as that of biliary colic. Morphine alters both the perception and reaction to pain. It raises the pain threshold and thus increases the capacity

to tolerate pain. Further, it alters the emotional reaction to pain.

Euphoria and sedation also contribute to its analgesic effects.

2. **Euphoria, sedation and hypnosis** Morphine produces a feeling of well-being termed *euphoria*. It is this effect which makes it an important drug of abuse. Rapid intravenous injection of morphine produces a warm flushing of the skin and an immensely pleasurable sensation in the lower abdomen lasting for about 45 seconds which is known as 'high', 'rush' or 'kick'. The person loses rational thinking and is lost in colourful day dreams. It also produces drowsiness, a calming effect, inability to concentrate, feeling of detachment and indifference to surroundings.

The effects of morphine may not be pleasurable in all. A person has to learn to perceive its pleasurable effects. It may produce dysphoria in some.

3. **Respiration** Morphine produces significant respiratory depression. It directly depresses the respiratory centre in the brainstem. This action is dose dependent. It depresses all phases of respiratory activity - rate and tidal volume. It may

also alter the rhythm to produce irregular and periodic breathing. Death from morphine poisoning is almost always due to respiratory arrest.

Morphine suppresses neurogenic (originating in RAS), chemical (hypercapnoeic) and hypoxic drive in the order. The respiratory centre is insensitive to increased plasma CO₂ concentration. With toxic doses, breathing is maintained by hypoxic drive.

Sedation and indifference to surroundings add to the depression.

4. *Cough centre* It directly depresses the cough centre and thereby suppresses cough.
5. *Nausea and emesis* Morphine directly stimulates the CTZ in the medulla causing nausea and vomiting. In higher doses it depresses the vomiting centre and hence there is no vomiting in poisoning. Therefore, emetics should not even be tried in morphine poisoning.
6. *Pupils* Morphine produces miosis resulting in a characteristic pinpoint pupil in high doses. This is due to stimulation of (EW) nucleus of the third cranial nerve. Thus by a central effect it produces miosis. Hence morphine used as eyedrops does not produce miosis.
7. *Vagus* Morphine stimulates vagal centre causing bradycardia.
8. *Heat regulation* Opioids shift the equilibrium point of heat-regulating centre so that body temperature falls slightly.
9. *Excitatory effect* In high doses opioids produce convulsions. They may increase the excitability of the spinal cord.

Cardiovascular System

In therapeutic doses, morphine produces hypotension by:

- direct peripheral vasodilatation
- inhibition of baroreceptor reflexes

In higher doses it causes depression of the vasomotor centre and histamine release both contributing to a fall in BP. Postural hypotension and fainting may occur.

GIT

Opioids decrease the motility of the gut.

Stomach Gastric motility is decreased resulting in increased gastric emptying time. Oesophageal reflux may increase. Gastric acid secretion is reduced. Opioids increase the tone of the antrum and first part of the duodenum which also contribute to delayed emptying by almost 12 hours and this can retard the absorption of orally given drugs.

Intestines Morphine diminishes all intestinal secretions, delays digestion of food in the small intestine; resting tone is increased. There can be spasms of the intestine. The tone of the sphincters is increased leading to spasm. The intestinal motility (propulsive) is markedly diminished. The resulting delay in the passage of the intestinal contents in the large intestine, together with reduced secretions and inattention to the sensory stimuli for defecation reflex - all contribute to produce marked constipation. The effects of morphine on the gut are by stimulation of μ and δ receptors in the gut.

Other Smooth Muscles

Biliary tract Morphine causes spasm of the sphincter of Oddi. Intrabiliary pressure rises and may cause biliary colic. Atropine partly antagonises this while opioid antagonists relieve it.

Urinary bladder and ureter Tone and amplitude of contractions of the ureter is increased; tone of external sphincter and volume of the bladder are increased. Opioids inhibit

urinary voiding reflex. All these result in urinary retention especially in the elderly male with prostatic hypertrophy.

Uterus No significant effect. May prolong labour in high doses.

Bronchi Morphine causes release of histamine from the mast cells leading to bronchoconstriction. This can be dangerous in asthmatics.

Neuroendocrine Effects

Morphine acts in the hypothalamus to inhibit the release of gonadotrophin-releasing hormone and CRF, thus decreasing blood levels of FSH, LH, ACTH and β -endorphins. Tolerance develops after long-term use. These effects are reversible on cessation of therapy.

Pharmacokinetics

Given orally, absorption of morphine is slow and incomplete. Morphine undergoes extensive first pass metabolism. Bioavailability is 20 to 40%. Some opioids are also given as rectal suppositories while highly lipid soluble opioids are available as transdermal preparation. Dose - Table 26.3.

Given subcutaneously, onset of action is in 15-20 min, peak effect - in 1 hr, duration of action is - 3-5 hr. Morphine is metabolised in the liver by glucuronide conjugation. The active metabolite morphine-6-glucuronide, is more potent than morphine and is excreted through the kidneys. Morphine undergoes enterohepatic circulation.

Adverse Effects

Morphine can produce a wide range of adverse effects like nausea, vomiting, dizziness, mental clouding, respiratory depression, constipation, dysphoria, urinary retention and hypotension.

Allergic reactions including skin rashes, pruritus and wheal at the site of injection of morphine may be seen. Morphine is a histamine liberator and this action is responsible for the allergic effects. Rarely intravenous injection can cause anaphylaxis due to the same reason. It is a drug of dependence.

Tolerance

Repeated administration of morphine results in the development of tolerance to some of its effects including respiratory depression, analgesia, sedation and euphoriant effects and other CNS depressant effects. Constipation and miosis show no tolerance. Though lethal dose of morphine is about 250 mg, addicts can tolerate morphine in grams. Patients in pain can also tolerate a higher dose of morphine. Cross-tolerance is seen among different opioids.

Tolerance is mainly pharmacodynamic, where the cells adapt to the effect of opioids - at the receptor level, though pharmacokinetic mechanisms like increased metabolism also contribute. An addict needs progressively higher doses to get his 'kick' or 'rush'.

Dependence

Opium has been a drug of addiction for many centuries. Its ability to produce euphoria makes it a drug of addiction. Opioids produce both psychological and physical dependence. Sudden cessation of opioids or administration of opioid antagonists produce significant withdrawal symptoms in such dependent individuals. Manifestations are lacrimation, sweating, yawning, anxiety, apprehension, restlessness, rhinorrhoea and tremors - seen 8-12 hr after the last dose. The person craves for the drug. As the syndrome progresses, fever, insomnia, abdominal colic,

severe sneezing, violent yawning, diarrhoea, blurring of vision due to mydriasis, hypertension, severe dehydration, 'goose-flesh', palpitation, prostration and cardiovascular collapse can occur. There is profound weakness, depression and irritability. 'Gooseflesh' is due to pilomotor activity; skin resembles that of a plucked turkey. Hence the word 'cold turkey' is used for symptoms due to abrupt withdrawal. Abdominal cramps, pain in the bones and muscles of the back and limbs are also characteristic.

In spite of all these disturbing symptoms, withdrawal symptoms are generally not life-threatening. Administration of a suitable opioid, dramatically and completely reverses the symptoms of withdrawal. Without treatment, symptoms disappear in 7-10 days.

Withdrawal in the Newborn

Babies born to mothers who were addicts prior to delivery - will also be dependent. Withdrawal symptoms seen are irritability, excessive crying, tremors, frantic suckling of

fists, diarrhoea, sneezing, yawning, vomiting and fever. Tincture of opium 0.2 ml /kg/3-4 hr is started at birth and gradually withdrawn.

Management of Addiction

Morphine is slowly withdrawn over several days and substituted by oral *methadone*.

Advantages of methadone administration are

1. Methadone is effective orally and by this route no 'kick' is experienced.
2. It is more potent, long - acting and prevents withdrawal symptoms because it is slowly released from the tissues.

The dose is adjusted as per the degree of dependence - 1 mg methadone for every 4 mg of morphine (once a day). Methadone is then gradually withdrawn.

Most addicts can be completely withdrawn from opioids in about 10 days though mild tolerable withdrawal symptoms persist. Symptoms like insomnia, malaise, restlessness, irritability, fatigue and GI hyperactivity may last up to several months.

Table 26.1: Compare and contrast aspirin and morphine

Features	Aspirin	Morphine
Chemistry	Acid (Acetyl Salicylic Acid)	Alkaloid
Natural Source	Bark of willow tree	<i>Papaver Somniferum</i>
Anti inflammatory action	Yes	No
Antipyretic, and uricosuric effects	Yes	No
Euphoria, Sedation	No	Yes
Abuse Potential	No	Yes
Effect on Respiration	Stimulant (in therapeutic doses)	Depressant
Mechanism of action	PG synthesis inhibition	Opioid receptor stimulation
Effect on pupil	Not significant	Miotic
Effect on stomach	↑ HCl secretion → Ulcerogenic	↓ Decrease secretions
Major action	Analgesic	Analgesic

Clonidine a central α_2 agonist can suppress some of the autonomic withdrawal symptoms like anxiety, nausea, vomiting and diarrhoea. It is given for 7 - 10 days and withdrawn over 3 - 4 days. Night time sedation with a hypnotic like *diazepam* is helpful.

Acute Morphine Poisoning

Acute morphine poisoning may be accidental, suicidal or homicidal. Lethal dose in non-addicts is about 250 mg but addicts can tolerate grams of morphine. Signs and symptoms include respiratory depression with shallow breathing, pin point pupils, hypotension, shock, cyanosis, flaccidity, stupor, hypothermia, coma and death due to respiratory failure and pulmonary oedema.

Treatment

1. Positive pressure respiration.
2. Maintenance of BP.
3. Gastric lavage with potassium permanganate to remove unabsorbed drug.
4. Specific antidote is naloxone - 0.4 - 0.8 mg IV repeated every 10-15 min.

Precautions and Contraindications

1. Avoid opioids in patients with respiratory insufficiency - COPD.
2. An attack of bronchial asthma can be precipitated by morphine.
3. In extremes of age - more susceptible to respiratory depression.
4. Head injury - morphine is contraindicated in head injury because:
 - (i) morphine increases CSF pressure by retaining CO_2 and thereby increases the intracranial tension.
 - (ii) causes marked respiratory depression.

- (iii) vomiting, miosis and mental clouding seen with morphine interfere with diagnosis and assessment of progress in head injuries.
5. In hypovolaemic shock, morphine further decreases the BP.
 6. Opioids potentiate CNS depressants.
 7. Undiagnosed acute abdomen - Morphine relieves pain and may interfere with the diagnosis. It induces vomiting and its spasmogenic effect may add to its drawbacks. Hence it can be administered only after the diagnosis is established - if necessary.

Other Opioids

Heroin or diamorphine or diacetyl morphine is converted to morphine in the body. It has higher lipid solubility because of which euphoric effects are faster and greater resulting in higher abuse potential. It has a strong smell of vinegar. Though it can be used as an analgesic, it is banned in most countries.

Levorphanol is similar to morphine but it is longer acting.

Codeine is a naturally occurring opium alkaloid. Codeine depresses the cough centre in subanalgesic doses. It is effective orally and is well-absorbed.

It is less potent (one-sixth) than morphine as an analgesic (60 mg codeine = 10 mg morphine).

It produces less respiratory depression and is less constipating. Codeine has less addiction liability and tolerance is uncommon.

Hence codeine is used as an antitussive. It is well-absorbed when given orally compared to morphine. Duration of action is 4-6 hours. 10 to 30 mg is the antitussive dose. About 10% of codeine is converted to morphine. Constipation is the most common side effect.

Uses Codeine is a commonly used antitussive. It is also available in combination with paracetamol for analgesia. It is to be given at bed time (CODOPLUS - Codeine 30 mg + Paracetamol 500 mg).

Papaverine is devoid of opioid and analgesic activity.

Noscapine is a naturally occurring opium alkaloid. In therapeutic doses, it has no significant actions on the CNS except for antitussive effects. Hence it has no disadvantages of opioids. In large doses it may cause bronchoconstriction due to the release of histamine. Dose: 15-30 mg, 3-4 times a day. Noscapine is highly effective and safe. The only adverse effect is nausea. It is used as a cough suppressant.

Several other centrally acting antitussives have been synthesized including, pholcodeine, and dextromethorphan.

Pholcodeine though structurally related to opioids, has no other opioid-like actions. It is as effective as codeine as an antitussive; has a long half-life and therefore can be given once a day.

Dextromethorphan has no analgesic or addictive properties. It acts centrally to elevate the threshold for coughing for which it is as effective as codeine. Toxicity is very low; extremely high doses cause CNS depression. Antitussive dose: 10 - 30 mg, 3 - 4 times a day.

Tramadol is a recently developed synthetic codeine analog. It is an effective analgesic but its mechanism of action is not clear. It is a weak opioid agonist. In addition it inhibits the reuptake of noradrenaline and serotonin in the CNS.

Adverse effects include drowsiness, dryness of mouth, sedation and nausea. Respiratory depression is mild. It is a drug of dependence. It may precipitate seizures.

It should be avoided in patients on MAO inhibitors because tramadol inhibits serotonin uptake.

Tramadol is used in acute and chronic pain, like postoperative pain and neuralgias.

Pethidine (Meperidine)

Pethidine is a phenylpiperidine derivative of morphine. Many of its actions resemble that of morphine Table 26.2. When compared to morphine:

- pethidine is 1/10 th as potent as morphine (100 mg pethidine = 10 mg morphine). However, efficacy as an analgesic is equal to morphine
- the onset of action is more rapid and duration of action is shorter
- it produces corneal anaesthesia
- it is not a good antitussive
- it is less constipating
- in some patients, it may cause dysphoria
- it also has anticholinergic effects which can cause dry mouth, and blurring of vision.
- in toxic doses, pethidine sometimes produces CNS stimulation with tremors, restlessness and convulsions instead of sedation. This is because of the toxic metabolite - norpethidine.

Adverse effects are similar to morphine except that constipation and urinary retention are less common.

Uses

Dose 25-100 mg IM/SC is the analgesic dose.

In pain Pethidine is used as an analgesic in visceral pain and also for other indications of morphine. Because of its better oral efficacy and less spasmogenic effect, pethidine is preferred to morphine.

During labour Given during labour, pethidine produces less respiratory depression in the

newborn when compared to morphine. Moreover it does not interfere with uterine contractions and labour and is therefore preferred to morphine for obstetric analgesia.

Preanaesthetic medication – Pethidine can also be used as preanaesthetic medication.

DERIVATIVES OF PETHIDINE

Fentanyl

Fentanyl is a pethidine congener.

Advantages

- It is about 100 times more potent than morphine as an analgesic.
- Fentanyl is highly lipid soluble and fast acting (maximum effect within 5 minutes.)
- Fentanyl has mild effects on the cardiovascular system. It slightly reduces HR and BP. Hence it is found to be safer than other opioids in cardiovascular surgeries.
- Transdermal patches of fentanyl are available which acts for 48 hours.
- Unlike morphine, fentanyl does not increase the intracranial pressure.
- Fentanyl is not a histamine liberator.
- It can be used in combination with droperidol, a neuroleptic agent to produce neuroleptanalgesia.

Because of the above advantages fentanyl is a commonly used opioid analgesic.

For neuroleptanalgesia the combination is given IV to produce sedation and intense analgesia without loss of consciousness. This state is maintained for 30-40 minutes as both have rapid and short-action (See page 128). A fixed dose combination is available with 0.05 mg fentanyl + 2.5 mg droperidol per ml. 5 ml is the dose used IV over 10 minutes. Patient is drowsy but responds to commands.

Uses

1. Neuroleptanalgesia is used for short surgical procedures especially in 'poor risk' patients.
2. Epidural fentanyl is used for postoperative and obstetric analgesia. For this morphine/fentanyl may be combined with local anaesthetics so that lower doses of both drugs are sufficient.
3. Fentanyl can also be used in chronic pain where opioid use is permissible.

Adverse Effects

Bolus doses of fentanyl cause muscle rigidity. This can be reduced by avoiding bolus doses. Other adverse effects include nausea, vomiting and respiratory depression.

Table 26.2: Compare and contrast morphine and pethidine

Features	Morphine	Pethidine
Source	Natural opium alkaloid	Synthetic
Potency	More potent	Less potent (1/10th of morphine)
Corneal anaesthesia	No effect	Corneal anaesthetic
Higher doses	Profound CNS depression	CNS stimulation (due to norpethidine)
Antitussive property	Good	Poor or nil
Constipation effect	Marked	Less
Analgesic dose	10 mg	100 mg
Anticholinergic effect	Absent	Present
Use during labour	Significant respiratory depression in the neonate	Less neonatal respiratory depression - hence preferred over morphine

Congeners of fentanyl are sufentanil, alfentanil and remifentanil. Alfentanil and remifentanil are faster acting (act within one minute) and recovery is rapid. They are used for short surgical procedures.

Methadone

Methadone a synthetic opioid, has actions similar to morphine. Its outstanding features are:

- It is an effective analgesic
- It is effective by oral route
- It has a long duration of action ($t_{1/2}$ 24 - 36 hours) and therefore effectively suppresses withdrawal symptoms in addicts.

Methadone is about 90% bound to plasma proteins; it is firmly bound to proteins in various tissues, including brain. After repeated administration, it gradually accumulates in tissues. When administration is discontinued, the drug is slowly released from these binding sites. This probably accounts for its milder withdrawal symptoms. As euphoric effects are less intense, abuse potential is less. Tolerance develops more slowly. Even in addicts, withdrawal symptoms are gradual in onset, less intense, but prolonged.

Preparation 10 mg inj, (2 mg/5 ml syrup) Dose - 10 mg oral or IM.

Uses

1. *Substitution therapy* In opioid dependence, 1 mg oral methadone is given for every 4 mg morphine.
2. *Opioid maintenance*: Gradually increasing doses of methadone is given orally to produce a high degree of tolerance. Such subjects do not experience the pleasurable effects of IV morphine, i.e. opioids are not pleasurable in them and they give up the habit.

3. Methadone can also be used as an *analgesic*.

LAAM (L - alpha - acetyl - methadol) is a derivative of methadone. L- alpha- acetyl-methadol is found to have longer duration of action than methadone so that it can be given three times a week. It is used to prevent withdrawal symptoms in addicts.

Dextropropoxyphene

Dextropropoxyphene is a congener of methadone. It binds to the opioid receptors and produces effects similar to morphine. It is less constipating, longer acting and has good oral efficacy. But dextropropoxyphene is an irritant when given parenterally. Large doses cause CNS stimulation. It also has abuse potential.

Uses

Used in mild to moderate pain. It is marketed in combination with aspirin.

Dextropropoxyphene 32 mg+aspirin 600 mg.

Ethoheptazine

Ethoheptazine is related to pethidine and has mild analgesic effects with low addiction potential. It is used orally are combination with NSAIDs for relief of pain.

Uses of Morphine and Its Congeners

Dose Morphine 10 to 20 mg IM/SC; 20 mg tablets of ethylmorphine are now available for oral use.

1. *Analgesic* Morphine is one of the most potent analgesics available. It affords *symptomatic relief of pain* without affecting the underlying disease. It is an excellent analgesic for severely painful conditions such as acute myocardial infarction, fractures, burns, pulmonary embolism, terminal stages of cancer, acute pericarditis, spontaneous pneumothorax and

postoperative pain. In excruciating pain, morphine can be given IV.

In *myocardial infarction*, morphine relieves pain and thereby apprehension. As a result reflex sympathetic stimulation is reduced and shock is minimized.

- Morphine is given with atropine to relieve *renal and biliary colic*. Atropine relieves spasm of the sphincter of oddi. Morphine relieves pain in biliary colic but may cause spasm of the sphincter of Oddi which in turn raises intra-biliary pressure. Hence atropine is given to relieve the spasm of the sphincter of Oddi.
- Since opiate receptors are present in the spinal cord, epidural morphine can be used to produce *epidural analgesia*. Such analgesia is segmental in distribution and there is no interference with motor function or autonomic changes and no systemic adverse effects. Small doses of morphine can produce profound analgesia for 12-24 hours.
- *Obstetric analgesia* Pethidine is preferred to morphine for this condition.
- Opioids can be liberally given to control pain of *terminal illness* like cancers.
- But opioids should *not be* freely used in case of other chronic pain due to their addiction liability.

Various alternative routes of administration are tried for opioids - in order to reduce their systemic effects and provide longer duration of analgesia particularly for patients with chronic pain. Morphine and other opioids are being tried as intraspinal infusion, rectal, transmucosal, transdermal administration and by inhalation. In patient controlled analgesia (PCA) with opioids, the patients decide their own need for the analgesic. By the press of a button, a specific dose

of the opioid is pushed through an intravenous device. Careful monitoring is needed to avoid over-dosage.

2. *As preanaesthetic medication* Morphine and pethidine are commonly used as preanaesthetic medication. They reduce anxiety, provide analgesia, allow smoother induction and reduce the dose of the anaesthetic required. But they have certain disadvantages:
 - Opioids depress respiration
 - Morphine precipitates bronchospasm and is dangerous in patients with poor respiratory reserve
 - They cause vasomotor depression
 - They may induce vomiting
 - They may interfere with pupillary response to anaesthesia because they cause miosis.
 - Postoperative urinary retention and constipation may be troublesome.
3. *Acute left ventricular failure* Morphine is used to alleviate the dyspnoea of LVF and pulmonary oedema in which the response to IV morphine may be dramatic. The mechanism is not clear. The relief may be due to:
 - (i) alteration in the patient's reaction to impaired respiratory function.
 - (ii) reduction in the work of the heart due to decreased fear and apprehension. Reduced anxiety decreases sympathetic stimulation which in turn decreases cardiac work.
 - (iii) cardiovascular effects like decreased PVR leading to shifting of blood from pulmonary to peripheral circulation, thereby reducing cardiac work load.

Morphine is contraindicated in bronchial asthma and pulmonary oedema due to respiratory irritants.

4. *Diarrhoea* Opioids are effective for the symptomatic treatment of diarrhoea.

Table 26.3: Dose, duration of action and preparations of opioid analgesics

Name	Dose (mg)	Duration of analgesia (hours)	Preparations*	Trade name
Morphine	20-40	4-5	10, 30 mg CR-Tabs	Morcontin Continus
Ethyl morphine	16-32	6-8	16 mg tab	Dionindon
Methadone	10	4-6	-----	-----
Pethidine	50-100	2-4	50 mg, 100 mg inj.	Pethidine
Fentanyl	0.05-0.2	1-2	50 mcg inj. TD Patch-release 25-75 mcg/hr.	Trofentyl
Sufentanil	0.02	1-2	-----	-----
Codeine	30-60	3-5	Codeine 30 mg+Paracetamol 500 mg tab	Codoplus
Dextropropoxyphene	60 q	4-6	60 mg caps	Parvodex
Pentazocine	30-60	3-4	30 mg inj. IM/SC 30 IV q 4-6 hr	Pentawin
Nalbuphine	10-15	3-6	-----	-----
Buprenorphine	0.3-0.6 IM/Slow IV q 6 - 8 hr	4-8	0.3 mg inj., 0.2 mg SL tab	Pentorel
Butorphanol	2	3-4	1,2 mg inj.	Butrum
Ethoheptazine	75	3-4	75 mg tab with aspirin 325 mg	Equagesic
Tramadol	50-100 IM q 4-6 hr	4-6	50,100 mg inj.	Urgendol
* Preparations available in India . IM–Intramuscular IV–Intravenous SC–Subcutaneous TD–Transdermal CR–Controlled release SL–Sublingual				

Synthetic opioids - diphenoxylate and loperamide are preferred as antidiarrhoeals.

5. *Cough* Though morphine is an effective antitussive, codeine is the preferred opioid for this purpose. But now many nonaddictive antitussives are available.
6. *Special anaesthesia*
 - High doses of morphine can be used IV to produce general anaesthesia.
 - Neuroleptanalgesia - fentanyl with droperidol can be used to produce neuroleptanalgesia.

- Morphine can be used epidurally for the relief of postoperative and chronic pain.

7. *Sedative* Morphine relieves anxiety in threatened abortion without affecting uterine motility. It is an useful sedative in the presence of pain.

MIXED AGONISTS AND ANTAGONISTS

They include - pentazocine, cyclazocine nalbuphine, buprenorphine, butorphanol and nalorphine.

Pentazocine

In an attempt to develop an analgesic with less addiction liability and low adverse effects, pentazocine was developed. Pentazocine is a κ receptor agonist.

- CNS effects of pentazocine are similar to morphine. 20 mg pentazocine = 10 mg morphine. Euphoria is seen only in low doses. With higher doses - above 60 mg dysphoria can occur due to κ receptor stimulation.
- Sedation and respiratory depression are less marked.
- It has weak antagonistic properties at μ receptors.
- Tolerance and dependence develop on repeated use.
- CVS - In contrast to morphine, pentazocine increases BP and heart rate and thereby increases cardiac work. It is therefore *not* suitable in MI.
- Biliary spasm and constipation are less severe.

Preparations Pentazocine can be given both orally and parenterally. It undergoes first pass metabolism.

Dose 50-100 mg oral; 30-60 mg IM (FORTWIN).

Adverse effects Sedation, sweating, dizziness, nausea, dysphoria with anxiety, nightmares and hallucinations which are unpleasant are seen above 60 mg. As it is an irritant, IM injection can be painful and cause sterile abscesses.

Uses

Pentazocine is a commonly used opioid analgesic especially in postoperative and chronic pain - abuse liability is less than morphine.

Cyclazocine is similar to pentazocine.

Nalbuphine

Nalbuphine is an agonist - antagonist - more potent than pentazocine. It is a good analgesic. Though it produces respiratory depression like morphine, it has a ceiling effect at 30 mg, i.e. an increase in dose beyond 30 mg does not increase respiratory depression further. Higher doses produce dysphoria.

Uses As analgesic - 10-20 mg IM.

Buprenorphine

Buprenorphine is a highly lipid soluble synthetic thebaine congener. It is a partial μ agonist, 25 times as potent as morphine. Though onset of action is slow, duration of analgesia is long. Other CNS effects are similar to morphine while respiratory depression is less marked. Patients exhibit lower degree of tolerance and dependence liability. Withdrawal syndrome appears late and is mild.

Dose 0.3-0.6 mg SC, IM or sublingual (oral not available).

Uses Chronic pain like in terminal cancer patients. Buprenorphine can also be used as a maintenance drug in opioid addicts as the withdrawal symptoms are mild.

Butorphanol is similar to pentazocine.

Nalorphine

Nalorphine is also an agonist - antagonist. At low doses, it is a good analgesic. But with increase in dose there is no increase in analgesia.

It causes dysphoria (κ agonist) and respiratory depression even in low doses. Hence it cannot be used as an analgesic. At high doses it acts as an antagonist and counters all the actions of opioids.

Uses Nalorphine may be used in acute opioid poisoning. It can also be used for the diagnosis of opioid addiction.

Newer Agonist-Antagonists**Meptazinol**

Meptazinol is a short acting agonist - antagonist with additional anticholinergic effects. It produces short duration analgesia with less respiratory depression and is therefore suitable for obstetric analgesia.

Dezocine

Dezocine is a partial agonist at μ receptors. Its analgesic actions are similar to morphine but respiratory depression does not increase with an increase in dose (ceiling effect).

OPIOID ANTAGONISTS**Naloxone**

Naloxone acts as a competitive antagonist to all types of opioid receptors. It is a pure antagonist. In normal individuals, it does not produce any significant actions. But in opium addicts, given IV, it promptly antagonises all the actions of morphine including respiratory depression and sedation and precipitates withdrawal syndrome. It also blocks the action of endogenous opioid peptides - endorphins, enkephalins and dynorphins. It blocks the analgesia produced by placebo and acupuncture. This suggests that endogenous opioid peptides are responsible for analgesia by these techniques.

Given orally it undergoes first pass metabolism and is metabolised by the liver. Hence it is given intravenously. Duration of action is 3-4 hours.

Dose 0.4 mg IV.

Uses

1. Naloxone is the drug of choice for morphine overdose.
2. It is also used to reverse neonatal asphyxia due to opioids used in labour.
3. Naloxone can also be used for the diagnosis of opioid dependence - it precipitates withdrawal symptoms.
4. Hypotension seen during shock could be due to endogenous opioids released during such stress. Naloxone has been found to be beneficial in reversing hypotension.

Naltrexone

Naltrexone is another pure opioid antagonist. It is

- more potent than naloxone
- orally effective
- has a longer duration of action of 1-2 days.

Uses

1. Naltrexone is used for 'opioid blockade' therapy in post addicts (50-100 mg/ day orally) so that even if the addicts take an opioid, they do not experience the pleasurable effects and therefore lose the craving.
2. Alcohol craving is also reduced by naltrexone and is used to prevent relapse of heavy drinking (See page 145).

Nalmefene

Nalmefene is orally effective and longer acting. It has better bioavailability and is not hepatotoxic. It is used in opioid overdose.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Nonsteroidal anti-inflammatory drugs are aspirin-type or non-opioid analgesics. In addition, they have anti-inflammatory, antipyretic and uricosuric properties - without addiction liability.

The medicinal effects of the bark of the Willow tree have been known since centuries. The active principle 'salicin' was isolated from the Willow bark. This salicin is converted to glucose and salicylic acid in the body. In 1875, sodium salicylate was first used in the treatment of rheumatic fever. After its anti-inflammatory and uricosuric properties were established, efforts were made to synthesize derivatives which were less expensive. Now they have replaced the natural ones in the market.

CLASSIFICATION

A. Nonselective COX Inhibitors

1. *Salicylic acid derivatives*
Aspirin, sodium salicylate, diflunisal
2. *Para-aminophenol derivatives*
Paracetamol
3. *Pyrazolone derivatives*
Phenylbutazone, azapropazone
4. *Indole acetic acid derivatives*
Indomethacin, sulindac

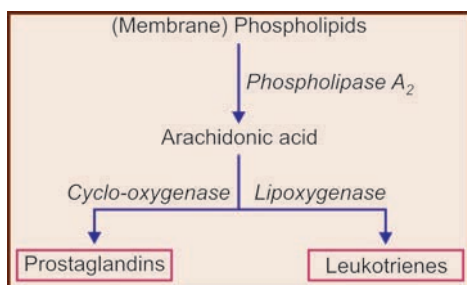
5. *Arylacetic acid derivatives*
Diclofenac, ketorolac, tolmetin
6. *Propionic acid derivatives*
Ibuprofen, fenoprofen, carprofen, naproxen, ketoprofen, flurbiprofen, oxaprozin
7. *Anthranilic acids (Fenamates)*
Flufenamic acid, mefenamic acid, enfenamic acid, meclofenamic acid
8. *Oxicams*
Piroxicam, tenoxicam, meloxicam
9. *Alkanones*
Nabumetone

B. Selective COX-2 Inhibitors

Nimesulide, celecoxib, rofecoxib, valdecoxib, etodolac

MECHANISM OF ACTION

During inflammation, arachidonic acid liberated from membrane phospholipids is converted to prostaglandins (PGs), catalysed by the enzyme cyclo-oxygenase (COX). These prostaglandins produce hyperalgesia - they sensitize the nerve endings to pain caused by other mediators of inflammation like bradykinin and histamine.



NSAIDs inhibit the PG synthesis by inhibiting the enzyme cyclo-oxygenase.

Aspirin is an irreversible inhibitor of COX (by acetylation) while the others are reversible competitive COX inhibitors. There are two forms of cyclo-oxygenase viz., COX-1 and COX-2 (see page 210). COX-1 is found in most of the normal cells (constitutive) and is involved in maintaining tissue homeostasis. COX-2 is induced in the inflammatory cells by cytokines and other mediators of inflammation. This COX-2 catalyses the synthesis of prostanoids which are the mediators of inflammation. Most NSAIDs inhibit both COX-1 and COX-2 while some newer agents like celecoxib and rofecoxib selectively inhibit only COX-2.

SALICYLATES

Salicylates are salts of salicylic acid, e.g. methyl salicylate, sodium salicylate, acetyl salicylic acid (aspirin). Aspirin is taken as the prototype.

Pharmacological Actions

1. Analgesia

Aspirin is a good analgesic and relieves pain of inflammatory origin. This is because PGs are formed during inflammation and they sensitize the tissues to pain and aspirin inhibits PG synthesis and thereby acts as an analgesic. Pain originating from the integumental structures like muscles, bones, joints, and pain in connective tissues is

relieved. But in vague visceral pain, aspirin is relatively ineffective.

The pain is relieved without euphoria and hypnosis. Hence there is no development of tolerance and dependence. But aspirin is a weak analgesic when compared to morphine. (Table 27.3)

2. Antipyretic action

In presence of fever, salicylates bring down the temperature to normal level. But, in normal individuals, there is no change in temperature.

In fever, pyrogen - a protein, circulates in the body and this increases the synthesis of PGs in the hypothalamus, thereby raising its temperature set point. The thermostatic mechanism in the hypothalamus is thus disturbed. Aspirin inhibits PG synthesis in the hypothalamus and resets the thermostat at the normal level bringing down the temperature.

Enhanced sweating and cutaneous vasodilatation promote heat loss and assist in the antipyretic action.

3. Anti-inflammatory action

At higher doses of 4-6 gm/day, aspirin acts as an anti-inflammatory agent. Signs of inflammation like tenderness, swelling, erythema and pain are all reduced or suppressed. But, the progression of the disease in rheumatoid arthritis, rheumatic fever or osteoarthritis is not affected.

Once again the mechanism involved is PG synthesis inhibition-PGs present in inflammatory tissues are responsible for oedema, erythema and pain. In addition, aspirin also interferes with the formation of chemical mediators of the kallikrein system. As a result, it decreases the adherence of granulocyte to the damaged vasculature, stabilizes lysosomes and decreases the migration of the polymorphonuclear leukocytes and macrophages into the site of inflammation.

4. Respiration

In therapeutic doses of 4-6 gm/day - salicylates increase consumption of oxygen by skeletal muscles. As a result there is increased CO_2 production. This increased CO_2 stimulates respiratory centre. Salicylates also directly stimulate the medullary respiratory centre. Both these actions increase the rate and depth of respiration. These effects are dose dependent.

As a result of this stimulation of respiration, plasma CO_2 is washed out leading to respiratory alkalosis. With toxic doses, the respiratory centre is depressed leading to respiratory failure.

5. Acid-base and electrolyte balance

In anti-inflammatory doses, salicylates produce significant respiratory stimulation - CO_2 is washed out resulting in respiratory alkalosis; pH becomes alkaline. This is compensated by increased excretion of HCO_3^- in urine accompanied by Na^+ , K^+ and water. pH then returns to normal. This stage is known as compensated respiratory alkalosis.

With toxic doses, salicylates depress the respiratory centre directly. As a result, CO_2 accumulates because more CO_2 is produced than is exhaled. Thus plasma CO_2 rises and pH decreases. Since the concentration of HCO_3^- is already low due to enhanced renal excretion, the change results in uncompensated respiratory acidosis. This is superimposed by metabolic acidosis caused by accumulation of acids.

Toxic doses also depress vasomotor centre. This vasomotor depression impairs renal function resulting in accumulation of strong acids of metabolic origin like lactic, pyruvic and acetoacetic acids.

The above effects are accompanied by dehydration due to:

- water lost in urine with HCO_3^- , Na^+ and K^+

- increased sweating
- water lost during hyperventilation.

Thus there is severe dehydration with acidosis.

6. Metabolic effects

Salicylates enhance the cellular metabolism due to uncoupling of oxidative phosphorylation. More of O_2 is used and more CO_2 is produced, especially in skeletal muscles, leading to increased heat production.

In toxic doses, hyperpyrexia, increased protein catabolism with resultant aminoaciduria and negative nitrogen balance are seen. Enhanced utilization of glucose leads to mild hypoglycaemia. But in toxic doses, hyperglycaemia occurs due to central sympathetic stimulation which increases adrenaline levels.

7. Gastrointestinal tract

Aspirin is a gastric irritant. Irritation of the gastric mucosa leads to epigastric distress, nausea and vomiting. Aspirin also stimulates the CTZ to produce vomiting.

Erosive gastritis, mucosal congestion, gastric ulceration and GI bleeding resulting in malaena and occasionally haematemesis can occur particularly in higher doses.

Mechanism of Action

- (i) In the acidic pH of the stomach, salicylates remain unionised. These drug particles adhere to the mucosa producing irritation. These particles also promote local back diffusion of acid.
- (ii) Aspirin decreases prostaglandin synthesis. PGs inhibit gastric acid secretion, increase mucus production and act as cytoprotectives in gastric mucosa. This defense mechanism is lost due to PG inhibition.

The above actions make aspirin ulcerogenic. In addition, it decreases platelet

aggregation which also increases the tendency to bleed.

With soluble aspirin, gastric irritation is less. The selective COX-2 inhibitors cause less gastric irritation.

8. CVS

In therapeutic doses no significant cardiovascular effects are seen. In toxic doses it depresses the VMC and thus depresses the circulation.

9. Immunological effects

In higher doses, salicylates suppress several antigen-antibody reactions including inhibition of antibody production, Ag-Ab aggregation and antigen induced release of histamine. These effects might also contribute to the beneficial effects in rheumatic fever.

10. Uric acid excretion

Uric acid is excreted by secretion from the distal tubules. In a dose of 1-2 gm/day, aspirin increases plasma urate levels by urate retention because it interferes with urate secretion by the distal tubules.

Large doses of > 5 gm/day increase urate excretion because it inhibits reabsorption of urate by proximal tubule causing uricosuria. But, its uricosuric effect cannot be used therapeutically because high doses are required and such doses result in prominent adverse effects.

11. Blood

Even in small doses aspirin irreversibly inhibits platelet cyclooxygenase and thereby TXA_2 synthesis by the platelets. It therefore interferes with platelet aggregation and prolongs the bleeding time. Even a single dose can irreversibly inhibit TXA_2 synthesis which is for the life of the platelets (8-11 days). As platelets cannot synthesize proteins which means COX cannot be regenerated, fresh platelets have to be formed to restore TXA_2 activity. Moreover aspirin inhibits platelet COX in the portal circulation itself and therefore even small doses (40 mg daily) of

aspirin is adequate for its antiplatelet aggregatory effect.

12. Local effects

Salicylic acid when applied locally is a keratolytic. It also has mild antiseptic and fungistatic properties. Salicylic acid is also an irritant for the broken skin.

Pharmacokinetics

Salicylates being acidic drugs are absorbed from the stomach and the upper small intestine. But aspirin as such is poorly soluble, hence not well-absorbed. When administered as microfine particles, absorption increases. Thus particle size, pH of the GIT, solubility of the preparation and presence of food in the stomach influence the absorption.

Salicylic acid and methylsalicylate are absorbed from the intact skin. They are extensively bound to plasma proteins. Aspirin is deacetylated in the liver, plasma and other tissues to release salicylic acid which is the active form. Plasma $t_{1/2}$ of aspirin is 3-5 hours. Elimination is dose dependent. It follows first order kinetics in small doses and zero order kinetics in higher doses. Therefore in anti-inflammatory doses, $t_{1/2}$ increases to 12 hr. Salicylates are excreted in urine.

Adverse Effects

Analgesic doses are generally well tolerated but anti-inflammatory doses are usually associated with adverse effects especially when used over a long period.

- *GI tract* Nausea, epigastric distress, vomiting, erosive gastritis, peptic ulcer, increased occult blood loss in stools are common.
- *Allergic reactions* are not common and may be manifested as rashes, urticaria, photo sensitivity, rhinorrhoea, angio-oedema and asthma especially in those with a history of allergies.

As aspirin inhibits only cyclo-oxygenase pathway, arachidonic acid is available for conversion by lipoxygenase pathway into leukotrienes. Leukotrienes are powerful bronchoconstrictors. Hence aspirin can precipitate bronchial asthma in some individuals. Of the currently available NSAIDs, diclofenac and indomethacin inhibit the synthesis of both PGs and LTs.

- **Haemolysis:** Salicylates can cause haemolysis in patients with G_6PD deficiency.
- **Nephrotoxicity:** Almost all NSAIDs can cause nephrotoxicity after long-term use. Salt and water retention and impaired renal function can occur.
- **Hepatotoxicity** can also occur when high doses of NSAIDs are used over a long period. Plasma levels of liver enzymes are raised.
- **Reye's syndrome** seen in children is a form of hepatic encephalopathy which may be fatal. It develops a few days after a viral infection especially influenza and varicella. An increased incidence of this syndrome has been noted when aspirin is used to treat fever. Hence aspirin is contraindicated in children with viral fever.
- **Pregnancy and infancy** Aspirin when taken at term delays the onset of labour due to inhibition of PG synthesis (PGs play an important role in the initiation of labour). Premature closure of ductus arteriosus may occur in the foetus resulting in portal hypertension. It can also increase postpartum bleeding due to inhibition of platelet aggregation.
- **Salicylism** Higher doses given for a long time as in treatment of rheumatoid arthritis may cause chronic salicylate intoxication termed 'Salicylism'. The syndrome is characterised by headache, vertigo, dizziness, tinnitus, vomiting,

mental confusion, diarrhoea, sweating, difficulty in hearing, thirst and dehydration. These symptoms are reversible on withdrawal of salicylates.

Acute salicylate intoxication Poisoning may be accidental or suicidal. It is more common in children, 15-30 grams is the fatal dose of aspirin.

Symptoms and Signs

Dehydration, hyperpyrexia, GI irritation, vomiting, sometimes haematemesis, acid-base imbalance, restlessness, delirium, hallucinations, metabolic acidosis, tremors, convulsions, coma and death due to respiratory failure and CV collapse.

Treatment is Symptomatic and Includes:

1. Gastric lavage to eliminate unabsorbed drugs.
2. IV fluids to correct acid-base imbalance and dehydration.
3. Temperature is brought down by external cooling with alcohol or cold water sponges.
4. If haemorrhagic complications are seen, blood transfusion and vitamin K are needed.
5. The IV fluids should contain Na^+ , K^+ , HCO_3^- and glucose (to treat hypokalaemia and acidosis). Blood pH should be monitored.
6. In severe cases, forced alkaline diuresis with sodium bicarbonate and a diuretic like frusemide is given along with IV fluids. Sodium bicarbonate ionizes salicylates making them water soluble and enhances their excretion through kidneys.

Precautions and Contraindications

Peptic ulcer, liver diseases, bleeding tendencies and viral fever in children contraindicate the use of aspirin/salicylates

Pregnancy - Aspirin should be avoided in pregnancy because it can cause premature closure of the ductus arteriosus in the foetus. Treatment with NSAIDs should be stopped one week before any surgery because of the risk of bleeding due to antiplatelet effect.

Preparations

Preparations and dosage of salicylates (Table 27.1 and 27.2).

Uses

1. As analgesic

For headache, backache, myalgias, arthralgias, neuralgias, toothache and dysmenorrhoea. In headache PGs may be responsible for cerebral vasodilation. NSAIDs inhibit PG synthesis and relieve headache. - PG synthesis is responsible for dysmenorrhoea - aspirin effectively relieves pain. The NSAIDs are beneficial in a variety of painful conditions of integumental origin and all these are associated with increase prostaglandin synthesis.

2. Fever

NSAIDs are useful for the symptomatic relief of fever.

3. For inflammatory conditions

Aspirin is effective in a number of inflammatory conditions such as arthritis and fibromyositis.

4. Acute rheumatic fever

In a dose of 4-6 gm/day (100 mg/kg/day) in 4-6 divided doses, aspirin brings about a dramatic relief of signs and symptoms in 24 to 48 hr. The dose is reduced after 4-7 days and maintenance doses of 50 mg/kg/day are given for 2-3 weeks.

5. Rheumatoid arthritis

Aspirin relieves pain, reduces swelling and redness of joints in rheumatoid arthritis. Joint mobility improves, fever subsides and there is a reduction in morning stiffness. But NSAIDs do not alter the progress of the disease. The relief is only symptomatic.

Dose: 4-6 gm/day in 4-6 divided doses.

6. Osteoarthritis

NSAIDs provide symptomatic relief in osteoarthritis.

7. Postmyocardial infarction and post-stroke
Aspirin inhibits platelet aggregation and this may lower the incidence of reinfarction in a low dose of 50 to 300 mg/day. It also decreases the incidence of transient ischaemic attacks (TIA) and stroke in such patients.

Table 27.1: Preparations and dosage of salicylates

Drug	Preparation	Dose
Aspirin	300, 350 tab (ASABUF); DISPRIN (Aspirin 350 mg and Calcium carbonate 105 mg)	Analgesic - 300-600 mg every 6-8 hr Anti-inflammatory - 4-6 gm/day Antiplatelet effects - 75-300 mg/day
Sodium salicylate	325, 650 mg tablets	325-650 mg every 4-8 hr
Salicylic acid	2% ointment; Whitfield's ointment- - Salicylic acid 3% - Benzoic acid 6%	For topical use
Methylsalicylate (Oil of wintergreen)	Ointment/liniment for topical use	As counter irritant
Diflunisal	250, 500 mg tab (DOLOBID)	250 mg every 8-12 hr

Low dose aspirin is also given to patients with angina pectoris with the hope of preventing MI in such patients.

It is also given in deep vein thrombosis to prevent recurrence.

8. Miscellaneous uses

- (i) To delay labour—Since PGs are involved in the initiation of labour, aspirin delays labour due to PG synthesis inhibition. But such use is associated with the risk of increased bleeding and premature closure of the ductus arteriosus.
- (ii) Some studies suggest that long-term use of aspirin at low doses is associated with a lower incidence of colon cancer.
- (iii) Patent ductus arteriosus (PDA): Aspirin may be given to bring about closure of PDA in the newborn.
- (iv) Excess production of renal PGs is thought to be responsible for Bartter's

syndrome characterised by raised plasma renin and aldosterone with hypokalemia. NSAIDs are useful in such patients.

- (v) Aspirin 60-100 mg daily is recommended in pregnant women with 'high risk' of hypertension. PGs are involved in the genesis of eclampsia and hypertension. Hence NSAIDs are useful in lowering BP in such patients.

9. Local

Salicylic acid is used as a keratolytic, fungistatic and mild antiseptic. Methylsalicylate is a counter-irritant used in myalgias. Mesalamine is used in inflammatory bowel disease.

Drug Interactions

- Salicylates compete for protein binding sites and displace drug molecules resulting in toxicity with warfarin, heparin,

Table 27.2: Topical preparations of NSAIDs

NSAID	Preparation	Brand Name
Salicylic acid	6 % W/W oint	KERALIN with hydrocortisone acetate and benzoic acid
	3 % oint	MYCODERM with benzoic acid and menthol
	2.2 % eardrops	METHAZIL with 6% methanol
Diclofenac diethyl ammonium	1.16 % gel	VOVERAN emulgel, RELAXYL gel, INAC gel
Piroxicam	0.5 % gel	DOLONEX gel, PIROX gel
Ibuprofen	50 mg gel methyl salicylate and menthol	ACKS gel with mephenisin,
Flurbiprofen	0.03% W/V eyedrops	OCUFLUR
Indomethacin	1% W/V eyedrops	INDOCAP ophthalmic drops
Naproxen	10% gel	XENOLID gel
Ketorolac tromethamine	0.5% W/V Eyedrops	KETANOV eyedrops KETLUR
Nimesulide	10 mg gel	NIZU gel with menthol 50 mg and Methyl salicylate 100 mg
Rofecoxib	1% gel	ROFIZ gel, ROFECOXIB 1%.

naproxen, phenytoin and sulfonylureas. Inhibition of platelet aggregation may increase the risk of bleeding with oral anticoagulants.

- In low doses salicylates can counter the uricosuric actions of probenecid by decreasing uric acid excretion.

Diflunisal

Diflunisal is a difluorophenyl derivative of salicylic acid. Diflunisal is 3-4 times more potent than aspirin as an anti-inflammatory agent but is a poor antipyretic due to poor penetration into CNS. Gastrointestinal and antiplatelet effects are less intense than aspirin. Side effects are fewer.

Uses Osteoarthritis, strain and sprains initial dose 500-1000 mg followed by 250 bd/tid.

PARA-AMINOPHENOL DERIVATIVES

Paracetamol (acetaminophen)

Phenacetin was the first drug used in this group. But, due to severe adverse effects it is now banned.

Paracetamol, a metabolite of phenacetin is found to be safer and effective.

Actions

Paracetamol has analgesic, good antipyretic and weak anti-inflammatory properties. Due to weak PG inhibitory activity in the periphery, it has poor anti-inflammatory actions.

Paracetamol is active on cyclo-oxygenase in the brain which accounts for its antipyretic action. In the presence of peroxides which are present at the site of inflammation, paracetamol has a poor ability to inhibit cyclo-oxygenase. It does not stimulate respiration, has no actions on acid-base balance, cellular metabolism, cardiovascular

system and platelet function; it is not a uricosuric agent and gastric irritation is mild.

Pharmacokinetics

Paracetamol is well-absorbed orally and 30% protein bound; it is metabolised by the hepatic microsomal enzymes: by glucuronide conjugation (60%) and glutathione conjugation (20%).

Adverse Effects

In antipyretic doses, paracetamol is safe and well-tolerated. Nausea and rashes may occur. But when large doses are taken, *acute paracetamol poisoning* results. Children are more susceptible because their ability to conjugate by glucuronidation is poor. 10-15 grams in adults cause serious toxicity. Symptoms are - nausea, vomiting, anorexia and abdominal pain during first 24 hours. Paracetamol is hepatotoxic and causes severe hepatic damage. Manifestations are seen within 2-4 days and include increased serum transaminases, jaundice, liver tenderness and prolonged prothrombin time which may progress to liver failure in some patients. Hepatic lesions are reversible when promptly treated.

Nephrotoxicity may result in acute renal failure in some.

Mechanism

A small portion of paracetamol is metabolised to a highly reactive intermediate - N-acetylbenzoquinone-imine which is detoxified generally by conjugation with glutathione. But when large doses of paracetamol are taken, hepatic glutathione is depleted and the toxic metabolite binds to sulphydryl groups in hepatic proteins resulting in hepatic necrosis.

Chronic alcoholics and infants are more prone to hepatotoxicity.

Treatment

Stomach wash is given. Activated charcoal prevents further absorption. Antidote is-N-acetylcysteine (150 mg/kg IV infusion over 15 min repeated as required; oral loading dose - 140 mg/kg followed by 70 mg/kg every 4 hr - 17 doses) - more effective when given early. N-acetylcysteine partly replenishes the glutathione stores of the liver and prevents binding of toxic metabolites to the cellular constituents.

Uses

- Paracetamol is used as an analgesic in painful conditions like toothache, headache and myalgia
- As an antipyretic
- Chronic pulpitis, periodontal abscess, post-extraction - paracetamol is used with ibuprofen.

PYRAZOLONE DERIVATIVES

Phenylbutazone

Phenylbutazone has good anti-inflammatory activity, is more potent, but has poorer analgesic and antipyretic effects. It is a uricosuric agent.

Phenylbutazone causes retention of Na⁺ and water. Thus after 1-2 weeks of use oedema results. It can also precipitate congestive cardiac failure.

Pharmacokinetics

Phenylbutazone is completely absorbed orally; IM injection is not recommended because its absorption is slow as it binds to local tissue proteins and also causes local tissue damage. It is 98% bound to plasma proteins; $t_{1/2}$ is 60 hr.

Dose 100-200 mg, BD. Small doses may be given 3-4 times a day to avoid gastric irritation.

Adverse Effects

- Phenylbutazone is more toxic than aspirin and is poorly tolerated - dyspepsia, epigastric distress, nausea and vomiting are common. Peptic ulceration and diarrhoea may occur. Oedema is a limiting factor and may precipitate CCF.
- Hypersensitivity reactions like rashes, serum sickness, stomatitis, hepatitis, nephritis, dermatitis and jaundice can occur. Phenylbutazone may cause serious haematological complications such as bone marrow depression, aplastic anaemia, agranulocytosis and thrombocytopenia.
- It may inhibit iodine uptake by thyroid, resulting in hypothyroidism and goitre on long-term use.
- CNS effects like insomnia, vertigo, optic neuritis, blurring of vision and convulsions may be encountered.

Because of its toxicity, phenylbutazone is withdrawn from the market in many western countries.

Uses

1. Rheumatoid arthritis
2. Ankylosing spondylitis
3. Osteoarthritis
4. Gout - phenylbutazone produces satisfactory relief from pain and inflammation in acute attacks
5. Other musculoskeletal disorders.

Azapropazone is structurally related to phenylbutazone but is less likely to cause agranulocytosis; $t_{1/2}$ is 12-16 hours.

Metamizol is a potent analgesic and antipyretic, but poor anti-inflammatory agent and has no uricosuric properties (ANALGIN, NOVALGIN) Dose: 500 mg 3-4 times a day.

It offers no advantages over aspirin. Not recommended in children upto 6 years.

Propiphenazone is similar to metamizol.

Dose 300-600 mg 3-4 times a day (SARIDON).

INDOLE ACETIC ACID DERIVATIVES

Indomethacin is a potent anti-inflammatory agent, antipyretic and good analgesic. It is well-absorbed, 90% bound to plasma proteins; $t_{1/2}$ - 4-6 hr.

Dose 25-50 mg b.d-t.d.s.

Adverse effects are high; gastrointestinal irritation with nausea, GI bleeding, vomiting, diarrhoea and peptic ulcers can occur.

CNS effects include headache, dizziness, ataxia, confusion, hallucinations, depression and psychosis.

Hypersensitivity reactions like skin rashes, leukopenia, and asthma in aspirin sensitive individuals. It can also cause bleeding due to decreased platelet aggregation and oedema due to salt and water retention.

Drug interactions Indomethacin blunts the diuretic action of furosemide and the antihypertensive action of thiazides, furosemide, β -blockers and ACE inhibitors by causing salt and water retention.

Uses (Table 27.3)

- Rheumatoid arthritis
- Gout
- Ankylosing spondylitis
- Psoriatic arthritis
- For closure of patent ductus arteriosus.

Sulindac has weaker analgesic, antipyretic and anti-inflammatory actions but is less toxic. Does not antagonize the diuretic and antihypertensive actions of thiazides. It may be used as an alternative drug for inflammatory conditions.

ARYLACETIC ACID DERIVATIVES

Diclofenac is an analgesic, antipyretic and anti-inflammatory agent. Its tissue penetrability

is good and attains good concentration in synovial fluid which is maintained for a long time. Adverse effects are mild.

Dose 50 mg bd-tds. Gel is available for topical application (INAC GEL). Ophthalmic preparation is available for use in postoperative pain.

Uses

1. Treatment of chronic inflammatory conditions like rheumatoid arthritis and osteoarthritis.
2. Acute musculoskeletal pain, painful dental lesions.
3. Postoperatively for relief of pain and inflammation.

Ketorolac is another PG synthesis inhibitor having good analgesic and anti-inflammatory properties. It is used for its analgesic properties to relieve postoperative pain. It is mostly used parenterally though it can also be given orally.

PROPIONIC ACID DERIVATIVES

Ibuprofen is better tolerated than aspirin. Analgesic, antipyretic and anti-inflammatory efficacy is slightly lower than aspirin. It is 99% bound to plasma proteins.

Adverse effects are milder when compared to other NSAIDs and the incidence is low. Nausea, vomiting, gastric discomfort, CNS effects, hypersensitivity reactions, fluid retention are all similar but *less severe* than phenylbutazone or indomethacin.

Dose Ibuprofen - 400-800 mg TDS (BRUFEN) ibuprofen + paracetamol (COMBIFLAM)

Uses

1. As an analgesic in painful conditions.
2. In fever.
3. Soft tissue injuries, fractures, following tooth extraction, to relieve postoperative pain, dysmenorrhoea and osteoarthritis.
4. Gout.
5. Surgical removal of impacted tooth-a combination of ibuprofen with a skeletal muscle relaxant like chlorzoxazone is recommended.

Table 27.3: Properties of some commonly used NSAIDs

NSAID	Properties	Advantages	Uses
Aspirin	Good analgesic, antipyretic, anti-inflammatory and uricosuric agent	• Antiplatelet activity even in low doses • Powerful anti-inflammatory activity	As analgesic-headache backache, neuralgias, dysmenorrhoea; pyrexia, rheumatic fever, rheumatic, psoriatic and osteoarthritis, for antiplatelet activity in poststroke and post- MI; closure of PDA; to delay labour
Paracetamol	Good analgesic, antipyretic but poor anti-inflammatory	• Less gastric irritation	As analgesic in fever
Diclofenac	Analgesic, antipyretic, anti-inflammatory	• Good concentration in synovial fluid; • Adverse effects mild	Chronic inflammatory conditions; rheumatoid arthritis, osteoarthritis, acute musculoskeletal pain and postoperative pain; acute pulpitis and acute periapical abscess
Piroxicam	Analgesic, antipyretic, anti-inflammatory	• Long-acting (given once a day) • Less ulcerogenic • Better tolerated	Arthritis, musculoskeletal pain, postoperative pain
Phenylbutazone	Good anti-inflammatory; poor analgesic, antipyretic; salt and water retention causes oedema; more toxic than aspirin	• Powerful anti-inflammatory agent	Rheumatoid and osteoarthritis; gout, ankylosing spondylitis
Indomethacin	Good analgesic, anti-inflammatory and antipyretic but toxicity is high	• Potent anti-inflammatory and analgesic	Rheumatoid, psoriatic and osteoarthritis, gout, ankylosing spondylitis, closure of PDA
Ibuprofen	Analgesic, anti-inflammatory, antipyretic all actions milder than aspirin	• Adverse effects milder therefore better tolerated	As analgesic in painful conditions, antipyretic, soft tissue injuries, fractures, postoperative pain, arthritis and gout; chronic pulpitis, peridontal abscess, gingival abscess

ANTHRANILIC ACID DERIVATIVES

Fenamates are analgesic, antipyretic, anti-inflammatory drugs with less efficacy, and are more toxic; contraindicated in children. They should not be used for more than one week. They are not generally preferred.

Adverse effects GI side effects are similar to aspirin but GI bleeding is less. Diarrhoea is common.

Uses Analgesic in myalgias, dysmenorrhoea, (250-500 mg TDS).

OXICAMS

Piroxicam is an oxicam derivative. It is long-acting, has good anti-inflammatory, analgesic and antipyretic activity. No clinically significant drug interactions are seen; better tolerated as it is less ulcerogenic. It is a reversible COX inhibitor. Dose 20 mg OD. It is *long-acting*. Piroxicam is used for rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute musculoskeletal pain and postoperative pain and painful dental lesions. *Meloxicam* is similar to piroxicam but in lower doses it causes less gastric irritation than piroxicam. It is therefore better tolerated. Dose 7.5-15 mg once daily.

Many other oxicams are being developed with the idea of obtaining one which is nonulcerogenic. But most of them are prodrugs of piroxicam and in lower doses some of them are selective COX-2 inhibitors.

ALKANONES

Nabumetone is an anti-inflammatory agent with significant efficacy in rheumatoid arthritis and osteoarthritis. It shows a relatively low incidence of side effects, it is comparatively less ulcerogenic. It is a prodrug and also selectively inhibits COX-2 - both account for the low ulcerogenic potential.

It is used in rheumatoid and osteoarthritis.

SELECTIVE COX-2 INHIBITORS

Celecoxib, *rofecoxib* and *valdecoxib* are diaryl substituted compounds. They are highly selective COX-2 inhibitors. They have good anti-inflammatory, analgesic and antipyretic properties but do not affect platelet aggregation (Table 27.4).

They are better tolerated because of milder gastric irritation (due to COX-2 selectivity) - but more long term studies are needed.

Disadvantages

The coxibs can cause hypertension and oedema which can be troublesome in patients with cardiovascular problems. Studies have shown that use of coxibs can increase the risk of myocardial infarction and stroke. The exact cause is not known but could be because of inhibition of PGI₂ production without inhibiting TXA₂. This results in a pro-thrombotic effect leading to myocardial infarction and stroke. Because they are derivatives of sulphonamides, allergic reactions including Stevens-Johnson syndrome have been reported. Hence most coxibs have been with-drawn from the market. Celecoxib has been approved for use in osteoarthritis and rheumatoid arthritis in the lowest effective dose and for the shortest period possible.

Dose:

Celecoxib - anti-inflammatory - 100-200 mg once or twice daily.

Rofecoxib - 12.5-25 mg daily.

Valdecoxib-20 mg twice daily.

Other coxibs include etoricoxib, lumiracoxib and paracoxib. They have properties similar to other coxibs.

Nimesulide a sulfonamide compound is a sulfonanilide derivative. It is a weak inhibitor of PG synthesis with a higher affinity for COX-2 than COX-1. It inhibits leukocyte function, prevents the release of mediators and in addition has antihistaminic and

Table 27.4: Compare and contrast aspirin and celecoxib

Features	Aspirin	Celecoxib
1. Chemistry	Salicylic acid derivative	Sulfonamide derivative
2. COX inhibition	Nonselective (COX-1, COX-2)	Selective COX-2 inhibitor
3. Ulcerogenic effect on gastric mucosa	+++ (Significant)	+ Mild
4. $t_{1/2}$	2-3 hours (short)	6-12 hours (Long)
5. Effect on platelet function	Inhibits platelet aggregation	Does not
6. Risk of Reye's syndrome in children	Present	Nil
7. Risk of thrombosis, atherogenesis	Nil	Present
8. Cardiovascular toxicity	No significant effect	Risk of MI
9. Cerebrovascular toxicity	No significant effect	Risk of stroke
10. Use in post MI patients	Recommended	Contraindicated
11. Prominent action	Analgesic, antipyretic anti-inflammatory	Analgesic, antipyretic anti-inflammatory
12. P G synthesis	Inhibited	Inhibited

antiallergic properties. Nimesulide has analgesic, antipyretic and anti-inflammatory actions like other NSAIDs.

Nimesulide is well-absorbed orally, extensively bound to plasma proteins and has a $t_{1/2}$ of 3 hours. It is excreted by the kidney. Dose 50-100 mg BD

Adverse effects are mild; they are nausea, epigastric pain, rashes, drowsiness and dizziness. It is claimed to be better tolerated. Long-term use can cause hepatotoxicity.

Uses

Nimesulide is used as an analgesic, antipyretic and anti-inflammatory agent for short periods as in headache, toothache, myalgia, dysmenorrhoea, sinusitis, postoperative pain

and arthritis. It is beneficial in patients who develop bronchospasm with other NSAIDs. But because of the risk of hepatotoxicity, nimesulide is now banned.

ANTAGONISTS OF LEUKOTRIENE SYNTHESIS AND LEUKOTRIENE RECEPTORS

Zileuton, montelukast, pranlukast, docebenone, piriprost - Some of them inhibit 5-lipoxygenase preventing the synthesis of leukotrienes, while others act as competitive antagonists of LT receptor. They are useful in asthma and other inflammatory conditions.

Adverse effects Dyspepsia, diarrhoea and headache.

Drugs Used in Rheumatoid Arthritis and Gout

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic, progressive, autoimmune, inflammatory disease, mainly affecting the joints and the periarticular tissues. The antigen-antibody complexes trigger the pathological process. Mediators of inflammation released in the joints initiate the inflammatory process. The earliest lesion is vasculitis, followed by synovial oedema and infiltration with inflammatory cells. There is local synthesis of prostaglandins and leukotrienes. Prostaglandins cause vasodilation and pain. The inflammatory cells release lysosomal enzymes which cause damage to bones and cartilage.

Drugs used in the treatment of rheumatoid arthritis

1. NSAIDs
2. Disease modifying agents
Gold, d-penicillamine, chloroquine and hydroxychloroquine, sulphasalazine, TNF blocking drugs
3. Immunosuppressants
Methotrexate, cyclophosphamide, azathioprine, leflunomide
4. Adjuvants
Glucocorticoids

Nonsteroidal anti-inflammatory drugs are the first line drugs in RA. NSAIDs afford symptomatic relief but do not modify the course of the disease.

Disease modifying drugs (DMDs) are also called disease modifying anti-rheumatic drugs (DMARDs). These are the second line drugs and are reserved for patients with progressive disease who do not obtain satisfactory relief from NSAIDs. They are capable of arresting the progress of the disease and inducing remission in these patients. The effects of these drugs may take 6 weeks to 6 months to become evident and are therefore called slow-acting anti-rheumatic drugs (SAARDs).

Gold salts were introduced for the treatment of RA in 1920s. They are considered to be the most effective agents for arresting the disease process.

On treatment, a gradual reduction of the signs and symptoms are seen. It brings about a decrease in the rheumatoid factor and immunoglobulins.

Mechanism of action is not exactly known - but gold depresses cell-mediated immunity (CMI). Gold salts concentrate in tissues rich in mononuclear phagocytes, selectively accumulate in the lysosomes of synovial cells and other macrophages in the inflamed synovium. They alter the structure and functions of the macrophages, depress their migration and phagocytic activity. They also inhibit lysosomal enzyme activity. Thus gold salts depress CMI.

Preparations Aurothiomalate sodium and auronofin are given orally. Aurothioglucose is given parenterally.

Adverse effects Treatment with gold is associated with several adverse effects and only 60% of patients remain on treatment at the end of 2 years.

Adverse effects include:

1. *On skin and mucous membrane* Dermatitis, pruritus, stomatitis, pharyngitis, glossitis, gastritis, colitis and vaginitis. A grey blue pigmentation on exposed parts of the skin may be seen.
2. *Renal toxicity* Haematuria, glomerulonephritis.
3. *Nervous system* Encephalitis, peripheral neuritis.
4. *Liver* Hepatitis, cholestatic jaundice.
5. *Blood* Thrombocytopenia, leukopenia, agranulocytosis, aplastic anaemia.
6. *CVS* Postural hypotension.
7. *Lungs* Pulmonary fibrosis.

Contraindications Kidney, liver and skin diseases; pregnancy and blood dyscrasias.

Uses

1. *Rheumatoid arthritis*—gold is used in active arthritis that progresses despite an adequate course of NSAIDs, rest and physiotherapy. In most patients gold salts arrest the progression of the disease, improve grip strength, reduce morning stiffness and prevent involvement of unaffected joints.

Gold is also beneficial in:

2. Juvenile rheumatoid arthritis
3. Psoriatic arthritis
4. Pemphigus
5. Lupus erythematosus.

d-penicillamine is an analog of the amino acid cysteine and a metabolite of penicillin. It is a chelating agent that chelates copper. Its actions and toxicities are similar to gold but is less effective than gold. Hence it is not

preferred. It is used as an alternative to gold in early, mild and non-erosive disease.

Adverse effects include drug fever, skin rashes, proteinuria, leucopenia, thrombocytopenia, aplastic anaemia, a variety of autoimmune diseases including lupus erythematosus, thyroiditis and haemolytic anaemia. Anorexia, nausea, vomiting, loss of taste perception and alopecia may also be seen.

Chloroquine and hydroxychloroquine These antimalarial drugs are found to be useful in mild non-erosive rheumatoid arthritis. They induce remission in 50% of patients. They are less effective but are better tolerated than gold.

Mechanism of action is not exactly understood but they are known to depress cell-mediated immunity.

Toxicity Chloroquine and hydroxychloroquine accumulate in tissues leading to toxicity. The most significant side effect is the retinal damage on long-term use. This toxicity is less common and reversible with hydroxychloroquine which is therefore preferred over chloroquine in rheumatoid arthritis. Every 3 months eyes should be tested. Other adverse effects include myopathy, neuropathy and irritable bowel syndrome.

Sulphasalazine is a compound of sulphapyridine and 5-amino salicylic acid. In the colon, sulphasalazine is split by the bacterial action and sulphapyridine gets absorbed. This has anti-inflammatory actions though the mechanism is not known. Adverse effects include gastrointestinal upset and skin rashes.

TNF Blocking Agents

Cytokines, particularly tumour necrosis factor (TNF) play an important role in the process of inflammation. TNF produced by macrophages and activated T cells, acts through TNF receptors to stimulate the

release of other cytokines. TNF blocking drugs are found to be useful in rheumatoid arthritis.

Infliximab is a monoclonal antibody which specifically binds to human TNF. When given in combination with methotrexate, it slows the progression of rheumatoid arthritis. Adverse effects of the combination include increased susceptibility to upper respiratory infections, nausea, headache, cough, sinusitis and skin rashes.

Etanercept is a recombinant fusion protein that binds to TNF molecules. It is found to slow the progression of the disease in rheumatoid arthritis patients. It is also found to be useful in psoriatic and juvenile arthritis. Etanercept is also given with methotrexate and the combination has a higher efficacy. It can cause pain, itching and allergic reactions at the site of injection.

Immunosuppressants are reserved for patients with seriously crippling disease with reversible lesions after conventional therapy has failed. Among the immunosuppressants, methotrexate (see page 330) is the best tolerated. Weekly regimens of low oral doses are given.

Leflunomide is a prodrug. The active metabolite inhibits autoimmune T cell proliferation and production of auto-antibodies by B cells. Leflunomide is orally effective, and has a long $t_{1/2}$ of 5-40 days. Adverse effects include diarrhoea and raised hepatic enzymes.

Leflunomide is used with methotrexate in rheumatoid arthritis patients who do not respond to methotrexate alone.

Corticosteroids

Glucocorticoids (chap-55) have anti-inflammatory and immunosuppressant activity. They produce prompt and dramatic relief of symptoms but do not arrest the

progress of the disease. However, long-term use of these drugs leads to several adverse effects. Moreover, on withdrawal of glucocorticoids, there may be an exacerbation of the disease. Therefore glucocorticoids are used as adjuvants. They may be used to treat exacerbations. Low dose long-term treatment with prednisolone is used in some patients (5-10 mg/day).

Intra-articular corticosteroids are helpful to relieve pain in severely inflamed joints.

Diet and Inflammation

Clinical studies have shown that when patients of rheumatoid arthritis are given a diet rich in unsaturated fatty acids (such as marine fish), there is a decrease in morning stiffness, pain and swelling of the joints. Unsaturated fatty acids compete with arachidonic acid for uptake and metabolism. Many products of arachidonic acid metabolism are mediators of inflammation. Adequate consumption of marine fish should be recommended. For people who do not eat fish, eicosapentaenoic acid 1-4 gm/day may be given as tablets. It serves as an adjuvant.

Relevance in Dentistry

1. Treatment with gold can cause glossitis.
2. Gold, d-penicillamine, immunosuppressants and glucocorticoids depress immunity. Treatment of dental infection requires powerful antibiotics in such patients.

PHARMACOTHERAPY OF GOUT

Gout is a familial metabolic disorder characterised by recurrent episodes of acute arthritis due to deposits of monosodium urate in the joints and cartilage. There is an inherent abnormality of purine metabolism resulting in over production of uric acid—a major end product of purine metabolism. As

uric acid is poorly water soluble, it gets precipitated—especially at low pH and is deposited in the cartilages of joints and ears, subcutaneous tissues, bursae and sometimes in kidneys. An acute attack of gout occurs as an inflammatory reaction to crystals of sodium urate deposited in the joint tissue. There is infiltration of granulocytes which phagocytize the urate crystals and release a glycoprotein that causes joint destruction. The joint becomes red, swollen, tender and extremely painful.

Secondary hyperuricaemia may be drug induced or may occur in lymphomas and leukaemias. Gout may also be due to decreased excretion of uric acid.

Strategies in the treatment of gout is either to decrease the biosynthesis of uric acid or enhance the excretion of uric acid.

Drugs Used in Gout

In acute gout:

Colchicine, NSAIDs.

In chronic gout:

Uric acid synthesis inhibitor

Allopurinol

Uricosuric drugs

Probenecid, sulphapyrazone,
benzbromarone.

Colchicine is an alkaloid of *Colchicum autumnale*. It is a unique anti-inflammatory agent effective only against gouty arthritis. It is not an analgesic.

Actions In gout, colchicine is highly effective in acute attacks and it dramatically relieves pain within a few hours. It increases gut motility by neurogenic stimulation.

Mechanism of action Colchicine inhibits the migration of granulocytes into the inflamed area and the release of glycoprotein by them. Colchicine binds to micro-tubules and arrests cell division in metaphase.

Pharmacokinetics Colchicine is rapidly absorbed orally, metabolised in the liver and undergoes enterohepatic circulation.

Adverse effects are dose related. Nausea, vomiting, diarrhoea and abdominal pain are the earliest side effects and may be avoided by giving colchicine intravenously. Anaemia, leukopenia and alopecia may be seen. In high doses haemorrhagic gastroenteritis, nephrotoxicity, CNS depression, muscular paralysis and respiratory failure can occur.

Uses

1. Acute gout—colchicine 1 mg orally initially followed by 0.5 mg every 2-3 hours relieves pain and swelling within 12 hours. But diarrhoea limits its use.
2. Prophylaxis—Colchicine may also be used for the prophylaxis of recurrent episodes of gouty arthritis.

NSAIDs afford symptomatic relief in the treatment of gout. Indomethacin is the most commonly used agent in acute gout. Piroxicam, naproxen and other newer NSAIDs are also used. They relieve an acute attack in 12-24 hours and are better tolerated than colchicine. But NSAIDs are not recommended for long-term use due to their toxicity.

Allopurinol is an analog of hypoxanthine and inhibits the biosynthesis of uric acid.

Mechanism of action Purine nucleotides are degraded to hypoxanthine. Uric acid is produced as shown in Figure 28.1. Allopurinol and its metabolite alloxanthine both inhibit the enzyme xanthine oxidase and thereby prevent the synthesis of uric acid. The plasma concentration of uric acid is reduced.

Pharmacokinetics Allopurinol is 80% absorbed orally; $t_{1/2}$ of allopurinol is 2-3 hr; $t_{1/2}$ of alloxanthine is 24 hours.

Adverse effects are mild. Hypersensitivity reactions include fever and rashes. Gastrointestinal irritation, headache, nausea and dizziness may occur.

Attacks of acute gouty arthritis may be seen frequently during the initial months of treatment with allopurinol.

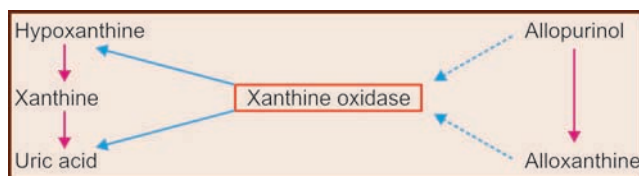


Fig. 28.1: Biosynthesis of uric acid

Drug interactions The anticancer drugs—6-mercaptopurine and azathioprine are metabolised by xanthine oxidase. Hence when allopurinol is used concurrently, the dose of these anticancer drugs should be reduced.

Uses Allopurinol is used in chronic gout and secondary hyperuricaemia. Initial dose is 100 mg/day and may be gradually increased to 300 mg/day depending on the response. Colchicine or an NSAID should be given during the first few weeks of allopurinol therapy to prevent the acute attacks of gouty arthritis. On treatment with allopurinol, tophi are gradually resorbed and the formation of renal stones are prevented. In patients with large tophaceous deposits, both allopurinol and uricosuric drugs can be given.

Uricosuric Drugs

Probenecid is an organic acid which was developed to inhibit the renal tubular

secretion of penicillin in order to prolong its action.

Probenecid blocks tubular reabsorption of uric acid and thereby promotes its excretion. It is well-absorbed and well-tolerated. Adverse effects include gastrointestinal irritation and skin rashes. Large amounts of water should be given to prevent the formation of renal stones.

Probenecid is indicated in chronic gout and secondary hyperuricaemia. Probenecid may also precipitate acute attacks of gout due to fluctuating urate levels.

Sulphinpyrazone a pyrazolone derivative is another uricosuric drug which has actions and adverse effects similar to probenecid. It is used in chronic gout.

Benzbromarone is a potent uricosuric drug which acts by inhibiting renal tubular reabsorption of uric acid. It is used as an alternative in patients allergic to other drugs. Benzbromarone can also be used in combination with allopurinol.

Drugs Used in Psychiatric Disorders

ANTI-PSYCHOTICS

Since ages man has sought the help of drugs to modify behaviour, mood and emotion. Psychoactive drugs were used both for recreational purposes and for the treatment of mental illnesses (Psyche = mind).

In 1931 Sen and Bose showed that *Rawolfia serpentina* is useful in the treatment of insanity. Electroconvulsive therapy (ECT) was introduced in 1937 for the treatment of depression. In 1950 chlorpromazine was synthesized in France and its usefulness in psychiatric patients was demonstrated in 1952. During the second half of the twentieth century, extensive research has been carried out in psychopharmacology and we now have several useful drugs in this branch of pharmacology.

Psychiatric conditions are broadly divided into psychoses, neuroses and personality disorders.

Psychoses are the more severe psychiatric disorders of the three and involve a marked impairment of behaviour, inability to think coherently, and to comprehend reality. Patients have no 'insight' into these abnormalities.

Psychoses could be due to:

- (i) An organic cause, i.e. there is a definable toxic, metabolic or pathological change—as following head injury.

- (ii) Functional or idiopathic disorders—where there is no definable cause like in schizophrenia, paranoia and affective disorders.

Schizophrenia (split mind) affects about 1% of population, starts at an early age and is highly incapacitating. It has a strong hereditary tendency and is characterised by delusions, hallucinations, irrational conclusions, interpretations and withdrawal from social contacts. Symptoms are grouped as positive and negative. *Positive symptoms* include delusions, hallucinations and disorders of thought while *negative symptoms* include poor concentration, social withdrawal, poverty of speech and lack of initiative and energy. Negative symptoms generally indicate poor prognosis and these symptoms do not respond to antipsychotic drugs. Patients with chronic schizophrenia have progressive shrinkage of the brain.

The pathology is not exactly understood but available evidence suggest overactivity of the neurotransmitters—mainly dopamine and probably others including glutamate and 5-HT. *Neuroses* are the milder forms of psychiatric disorders and include anxiety, mood changes, panic disorders, obsessions, irrational fears and reactive depression as seen following tragedies.

Personality disorders include paranoid, schizoid, histrionic, avoidant, antisocial and obsessive compulsive personality types.

Drugs used in psychiatric illnesses may be grouped as:

1. *Antipsychotics or neuroleptics* – used in psychoses.
2. *Antidepressant drugs* – used in affective disorders.
3. *Antianxiety drugs*

Psychotropic drugs are drugs used in mental illnesses - they are drugs capable of affecting the mind, emotions and behaviour.

Neuroleptic is a drug that reduces initiative, brings about emotional quietening and induces drowsiness. *Tranquilliser* is a drug that brings about tranquillity by calming, soothing and quietening effects. This is the older terminology. Neuroleptics or antipsychotics were called 'major tranquillisers' and antianxiety drugs were called 'minor tranquillisers'. These terminologies are no longer used.

ANTIPSYCHOTICS (NEUROLEPTICS)

Classification

1. *Classical/typical neuroleptics*
 - a. *Phenothiazines*–
Chlorpromazine, triflupromazine,
thioridazine, mesoridazine,
trifluoperazine, fluphenazine.
 - b. *Butyrophenones*–
Haloperidol, droperidol,
trifluoperidol, penfluridol.
 - c. *Thioxanthenes*–
Thiothixene, chlorprothixene,
flupenthixol
2. *Atypical neuroleptics*–
Clozapine, olanzapine,
risperidone, quetiapine,
ziprasidone, amisulpride,
remoxipride.
3. *Miscellaneous*–
Reserpine, loxapine,
pimozide.

Chlorpromazine (CPZ)

Mechanism of action– Typical neuroleptics act by blocking the dopamine D₂ receptors in the

CNS (Fig. 29.1). Since dopaminergic overactivity, mainly in the limbic area, is thought to be responsible for schizophrenia, DA receptor blockade helps. Some of them like phenothiazines also block D₁, D₃, and D₄ receptors. (There are 5 subtypes of dopamine receptors D₁ to D₅). Dopamine receptor blockade also is responsible for the classical side effects of these agents.

Pharmacological Actions

CNS Behavioural effects–in normal subjects CPZ reduces motor activity, produces drowsiness and indifference to surroundings. In psychotic agitated patients, it reduces aggression, initiative and motor activity, relieves anxiety and brings about emotional quietening and drowsiness. It normalises the sleep disturbances characteristic of psychoses.

Other CNS Actions

1. *Cortex* CPZ lowers seizure threshold and can precipitate convulsions in untreated epileptics.
2. *Hypothalamus* CPZ decreases gonadotrophin secretion and may result in amenorrhoea in women. It increases the secretion of prolactin resulting in galactorrhoea and gynaecomastia.
3. *Basal ganglia* CPZ acts as a dopamine antagonist and therefore results in extrapyramidal motor symptoms (drug induced parkinsonism).
4. *Brainstem* Vasomotor reflexes are depressed leading to a fall in BP.
5. *CTZ* Neuroleptics block the dopamine (DA) receptors in the CTZ and thereby act as antiemetics.

Autonomic nervous system The actions on the ANS are complex. CPZ is an alpha blocker. The alpha blocking potency varies with each neuroleptic. CPZ also has anticholinergic properties which leads to side effects like dryness of mouth, blurred vision, reduced sweating, decreased gastric motility,

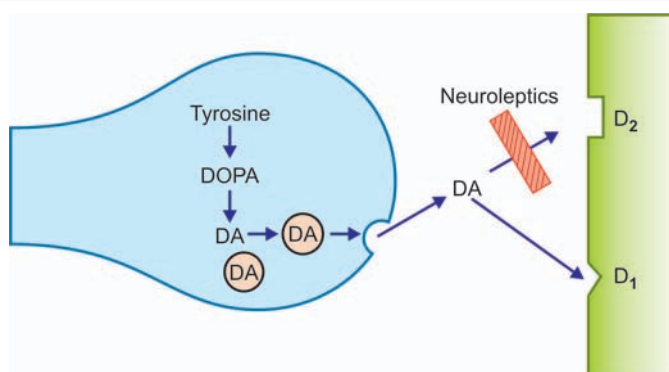


Fig. 29.1: Mechanism of action of neuroleptics. Neuroleptics block the dopamine D_2 receptors and act as antipsychotics

constipation and urinary retention. The degree of anticholinergic activity also varies with each drug.

CVS Neuroleptics produce orthostatic hypotension due to α blockade action and reflex tachycardia. CPZ also has a direct myocardial depressant effect like quinidine. *Local anaesthetic* CPZ has local anaesthetic properties—but is not used for the purpose since it is an irritant.

Kidney CPZ depresses ADH secretion and has weak diuretic effects.

Tolerance develops to the sedative and hypotensive actions while no tolerance is seen to the antipsychotic actions.

Pharmacokinetics

CPZ is incompletely absorbed following oral administration and also undergoes significant first pass metabolism (bioavailability is 30%). It is highly protein bound; has a $t_{1/2}$ of 20 to 24 hr and is therefore given once a day.

Adverse Reactions

Antipsychotics have a high therapeutic index and are fairly safe drugs.

1. *Cardiovascular and autonomic effects*—postural hypotension, palpitation, blurred vision,

dry mouth, constipation, nasal stuffiness and urinary retention result from blockade of α adrenergic and muscarinic receptors.

2. *CNS effects*—drowsiness and mental confusion are common, several neurological syndromes involving the extrapyramidal system are troublesome side effects.

They are -

Extrapyramidal Symptoms

- (i) *Acute dystonias* - Facial grimacing, tics, muscle spasms, protruding tongue and similar involuntary movements can occur in the first few days of starting antipsychotics especially the high potency ones like haloperidol. They respond to anticholinergics.
- (ii) *Parkinsonism* - Bradykinesia, tremors and rigidity including the typical parkinsonian face' may be noticed in the first few weeks. It responds to anticholinergic antiparkinsonian drugs.
- (iii) *Perioral tremors* - also called 'rabbit syndrome' may occur after several months of antipsychotic therapy, Anticholinergics are useful.
- (iv) *Akathesia*—is a feeling of intense discomfort which compels the person to be continuously moving, like -

constant walking. It necessitates a reduction in antipsychotic dosage and treatment with propranolol or other antianxiety drugs.

- (v) *Tardive dyskinesia*—appears after months or years of therapy and is characterised by involuntary movements of the face, tongue, eyelids, trunk and limbs. It can be disabling. Atypical antipsychotics like clozapine may be beneficial in such patients.
- (vi) *Malignant neuroleptic syndrome* is characterised by immobility, tremors and fever with autonomic effects like fluctuating blood pressure and heart rate. It can be fatal and requires immediate stopping of the neuroleptic. Dantrolene and bromocriptine may be useful.
- 3. *Endocrine disturbances*—gynaecomastia, amenorrhoea and galactorrhoea due to DA receptor blockade.
- 4. *Hypersensitivity reactions*—jaundice, agranulocytosis and skin rashes.

Drug Interactions

Neuroleptics enhance the sedative effects of CNS depressants, alpha blockers and of anticholinergic drugs. When combined with these groups of drugs, the effects may be additive.

Neuroleptics antagonise the actions of dopamine agonists and levodopa.

Uses

Neuroleptics are given orally. (Table 29.1). In acute psychosis they may be given intramuscularly and response is seen in 24 hr while in chronic psychosis it takes 2-3 weeks of treatment to demonstrate the beginning of obvious response.

1. *Psychiatric conditions* Psychoses including schizophrenia and organic brain

syndromes like delirium and dementia all respond to antipsychotics.

2. *Nausea, vomiting* CPZ is a good antiemetic and is used in vomiting due to radiation sickness and drug induced vomiting.
3. *Hiccough* CPZ can control intractable hiccough though the mechanism of action is not known.
4. *Other neuropsychiatric syndromes* Neuroleptics are useful in the treatment of several syndromes with psychiatric features like psychoses associated with chronic alcoholism, Huntington's disease and Gilles de La Tourette's syndrome.

Haloperidol is a potent antipsychotic with actions similar to chlorpromazine. It differs from chlorpromazine in that it has lesser incidence of autonomic side effects and is therefore preferred in older patients.

Haloperidol is useful in acute schizophrenia, and is the drug of choice in Gilles de la Tourette's syndrome and Huntington's disease.

Atypical Antipsychotics

The newer atypical antipsychotics like clozapine and others have the advantages of

1. Causing fewer side effects like less sedation
 2. Being effective in suppressing both positive and negative symptoms of schizophrenia
 3. Effective in resistant cases of psychoses.
- Clozapine* is an effective antipsychotic. It blocks the dopamine D₁ and D₄ receptors but has low affinity for D₂ receptors. Hence it has very low incidence of extrapyramidal side effects (EPS). Clozapine also blocks 5-HT₂, α adrenergic and muscarinic receptors.

Clozapine has the following advantages over conventional antipsychotics:

1. Very low incidence of EPS
2. Sedation is low.

3. No endocrine side effects no galactorrhoea and gynaecomastia.
4. It is effective in patients not responding to conventional antipsychotics.

Adverse effects: The most important disadvantage with clozapine is that it may cause agranulocytosis in some patients, which can be fatal. Hence its use should be restricted to patients not responding to other conventional drugs. Moreover, regular WBC counts are a must.

Clozapine can also cause sedation, weight gain and hypotension.

Olanzapine is similar to clozapine in actions and advantages except that, olanzapine does not cause agranulocytosis.

Quetiapine is an effective antipsychotic, similar in actions to clozapine. Drowsiness and postural hypotension are seen.

Risperidone blocks serotonin ($5HT_{2A}$) and dopamine (D_2) receptors. It is effective against both positive and negative symptoms of schizophrenia.

Table 29.1: Therapeutic dosage of commonly used antipsychotics

Drug	Antipsychotic dose in mg/day
Chlorpromazine	100-800
Triflupromazine	50-200
Thioridazine	100-400
Trifluoperazine	2-20
Fluphenazine	1-10
Haloperidol	2-20
Trifluoperidol	1-8
Flupenthixol	3-15
Loxapine	20-100
Clozapine	50-300
Olanzapine	2.5-10
Risperidone	2-12
Pimozide	2-6
Sertindol	4-24

Advantages

1. At low doses no EPS dysfunction.
2. Low sedation.

Ziprasidone is an effective antipsychotic with actions and mechanism of action similar to risperidone.

Amisulpride is a potent D_2 and D_3 antagonist. Its actions and advantages are similar to risperidone.

Risperine acts by depleting monoamines, i.e. NA and DA. It causes serious side effects including depression because of which it is now not preferred as an antipsychotic.

ANTIANXIETY DRUGS (ANXIOLYTICS)

Anxiety is tension or apprehension which is a normal response to certain situations in life. It is a universal human emotion. But when it becomes excessive and disproportionate to the situation, it becomes disabling and needs treatment.

Antianxiety Drugs Include

Benzodiazepines

Diazepam, chlordiazepoxide, lorazepam, alprazolam.

5-HT agonist-antagonists

Buspirone, gepirone, ipsapirone.

β -blockers

Propranolol.

Others

Meprobamate, hydroxyzine.

Benzodiazepines (Chap 22) have good antianxiety actions and are the most commonly used drugs for anxiety. They are CNS depressants. Alprazolam in addition has antidepressant properties.

Buspirone is an azapirone with good anxiolytic properties. It is a selective $5-HT_{1A}$ partial agonist. $5-HT_{1A}$ receptors are inhibitory autoreceptors and binding of buspirone inhibits the release of 5HT. Buspirone is also a weak D_2 antagonist. It is useful in mild to moderate anxiety. Antianxiety effect

develops slowly over 2 weeks. Unlike diazepam, it is not a muscle relaxant, not an anticonvulsant, does not produce significant sedation, tolerance or dependence and is not useful in panic attacks.

Buspirone is rapidly absorbed and metabolised in the liver.

Dose 5-15 mg OD or TDS.

Side effects are mild including headache, dizziness, nausea and rarely restlessness.

Uses Buspirone is used in mild to moderate anxiety and is particularly beneficial when sedation is to be avoided. Ipsapirone and gepirone are similar to buspirone.

β-blockers (Chap 12) In patients with prominent autonomic symptoms of anxiety like tremors, palpitation and hypertension, propranolol may be useful. β-blockers are also useful in anxiety inducing states like public speaking and stage performance. They can be used as adjuvants to benzodiazepines.

Others

Meprobamate has anxiolytic property but is not preferred now as it is less effective and causes high sedation.

Hydroxyzine is an antihistaminic with anxiolytic actions. But due to high sedation it is not preferred.

ANTIDEPRESSANTS

Affective disorders are a group of psychoses associated with changes of mood, i.e. depression and mania.

Depression is a common psychiatric disorder but the aetiology of it is not clear.

Depression could be

1. Unipolar
 - Reactive
 - Endogenous
2. Bipolar mood disorder or manic depressive illness.

Reactive depression is due to stressful and distressing circumstances in life.

Endogenous depression is major depression and results from a biochemical abnormality in the brain. Deficiency of monoamine (NA, 5HT) activity in the CNS is thought to be responsible for endogenous depression.

Symptoms are

- Emotional symptoms - sadness, misery, hopelessness, low self esteem, loss of interest and suicidal thoughts.
- Biological symptoms - fatigue, apathy, loss of libido, loss of appetite, lack of concentration and sleep disturbances.

Bipolar depression is characterised by alternate mania and depression. It is less common and is associated with a hereditary tendency. Mania can be considered opposite of depression with elation, over-enthusiasm, over-confidence, often associated with irritation and aggression.

Drugs Used in Affective Disorders are

Classification

1. *Tricyclic antidepressants (TCA)*–
Imipramine, desipramine, clomipramine, amitriptyline, nortriptyline, doxepin
2. *Selective serotonin reuptake inhibitors (SSRI)*–
Fluoxetine, fluoxamine, paroxetine, citalopram, sertraline,
3. *Monoamine oxidase (MAO) inhibitors* –
Phenelzine, tranylcypromine, isocarboxazid, moclobemide.
4. *Atypical antidepressants*
Trazodone, nefazodone, venlafaxine, bupropion, mianserine, mirtazapine, reboxetine.

Tricyclic Antidepressants

Pharmacological Actions

1. *CNS* In normal subjects, TCA cause dizziness, drowsiness, confusion and difficulty in thinking. In depressed

patients, after 2-3 weeks of treatment, elevation of mood occurs; the patient shows more interest in the surroundings and the sleep pattern becomes normal.

2. **CVS** Postural hypotension and tachycardia (due to blockade of α_1 adrenergic and muscarinic receptors) can be severe in overdosage.
3. **ANS** TCAs have anticholinergic properties and cause dry mouth, blurred vision, constipation and urinary retention.

Mechanism of Action

TCAs block the reuptake of amines (noradrenaline or 5-HT) into the presynaptic terminal and thereby prolong their action on the receptors (Fig. 29.2). Thus they potentiate amine neurotransmission in the CNS.

Pharmacokinetics

TCAs are rapidly absorbed, extensively protein bound and metabolised in the liver. They have a long $t_{1/2}$ and can be given once daily. On prolonged administration accumulation can occur resulting in cumulative toxicity.

Adverse Effects

Sedation, postural hypotension, tachycardia, sweating and anticholinergic side effects like dry mouth, constipation, blurred vision and urinary retention are relatively common. TCA may precipitate convulsions in epileptics; may cause hallucinations and mania in some patients. Many TCAs may also cause weight gain due to increased appetite.

Acute toxicity is manifested by (mimic symptoms of atropine poisoning) delirium, excitement, hypotension, convulsions, fever, arrhythmias, respiratory depression and coma.

Treatment Physostigmine is given to overcome atropine-like effects; sodium bicarbonate for acidosis, phenytoin for seizures and arrhythmias - with other supportive measures.

Tolerance and dependence—tolerance develops gradually to the sedative and anticholinergic effects over 2-3 weeks. Starting with a low dose and gradually increasing the dose minimises the side effects.

Following long-term treatment, TCAs should be gradually withdrawn, because

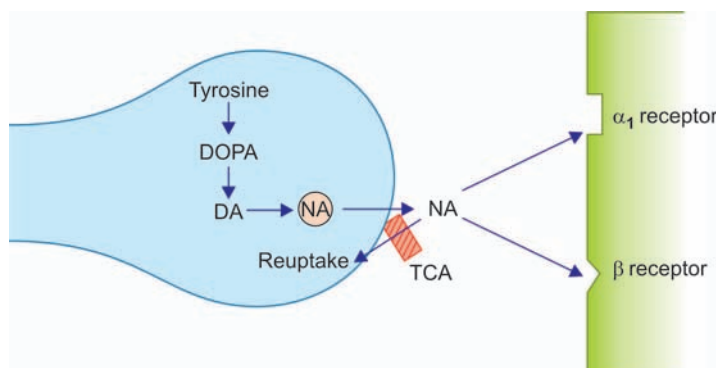


Fig. 29.2: Mechanism of action of tricyclic antidepressants. 80% of noradrenaline released into the synaptic cleft enters into the synaptic neuron by reuptake. This reuptake is blocked by TCA

withdrawal symptoms like headache, anxiety and chills can occur due to physical dependence.

Drug Interactions

1. Tricyclics potentiate sympathomimetics—even small amounts of adrenaline used with local anaesthetics can cause serious hypertension.
2. Highly protein bound drugs like phenytoin, aspirin and phenylbutazone displace TCAs from binding sites resulting in toxicity.
3. TCAs potentiate the effects of alcohol and other CNS depressants.

Selective Serotonin Reuptake Inhibitors (SSRI)

Include fluoxetine, fluoxetine, paroxetine, citalopram, and sertraline. Antidepressant actions and efficacy of SSRIs are similar to TCAs.

Mechanism of action—SSRIs block the reuptake of serotonin into the serotonergic nerve endings. Hence they enhance serotonin levels in these synapses (Fig. 29.3).

SSRIs have the following advantages over TCAs.

- Low cardiovascular side effects.
- Anticholinergic side effects are negligible.
- Less sedation.
- Preferred in elderly because of low anticholinergic effects (anticholinergic effects like constipation and urinary retention may be troublesome in the elderly).
- Safer in overdose (this is particularly advantageous in patients with depression who may have suicidal tendencies).
- Due to low side effect profile, SSRIs are generally well accepted by patients.

Adverse effects to SSRIs include nausea, vomiting, insomnia, anxiety and sexual dysfunction.

Among the SSRIs, fluoxetine is the most commonly used.

MAO Inhibitors

Monoamine oxidase (MAO) is an enzyme which metabolizes NA, 5-HT and DA. Drugs which inhibit this enzyme enhance the neuronal levels of NA, DA and 5HT. MAO exists as two isozymes - MAO_A and MAO_B. MAO_A is selective for 5-HT. Reversible and MAO_A selective inhibitors like moclobemide are now developed. Nonselective and

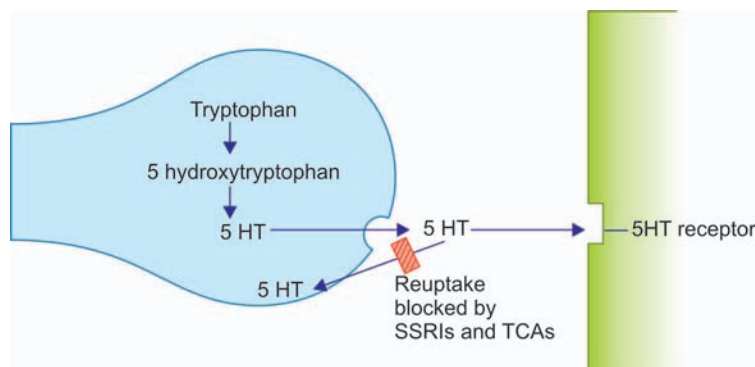


Fig. 29.3: Mechanism of action of SSRIs. They block the reuptake of serotonin and improve serotonergic transmission.

irreversible MAO inhibitors- phenelzine and tranylcypromine are associated with several side effects and risk of many food-drug interactions.

Tranylcypromine and Phenelzine:

- Irreversibly inhibit the enzyme MAO and enhance neuronal levels of noradrenaline, dopamine and 5-HT.
- Antidepressant actions develop slowly over weeks of treatment.
- Most of them are long acting and require 1-2 weeks for recovery of MAO activity after stopping the drug.
- Side effects are hypotension, weight gain, restlessness, insomnia (due to CNS stimulation), anticholinergic effects and rarely liver dysfunction.
- They interact with many drugs and food.
- Patients on MAO inhibitors taking tyramine containing foods like cheese, beer, wine, yeast, buttermilk and fish-develop severe hypertension and is known as 'cheese reaction.' Tyramine is normally metabolised by MAO in the gut wall. On inhibition of MAO by drugs, tyramine escapes metabolism and displaces NA from nerve endings leading to hypertension.
- Similar interaction with SSRIs can result in severe hypertension (serotonin syndrome).
- Because of the side effects and drug interactions, MAO inhibitors are not the preferred antidepressants.

Moclobemide is a reversible, competitive, selective MAO_A inhibitor. It is short acting and MAO activity recovers within 1-2 days after stopping the drug. It is found to be an effective antidepressant and has the advantages that it is not a sedative, does not produce cardiovascular and anticholinergic side effects. Hence it is well tolerated. No significant drug interactions are seen.

Adverse effects include nausea, insomnia, headache and dizziness.

Moclobemide is used in mild to moderate depression as an alternative to TCA.

Atypical Antidepressants

Atypical antidepressants include trazodone, bupropion, mianserin, nefazodone and mirtazapine.

Advantages

- Fewer side effects—particularly sedation and anticholinergic effects
- Safer in overdose
- Effective in patients not responding to TCA.

Trazodone is a weak serotonin reuptake inhibitor. It is short acting (t_{1/2} - 6 hr) and lacks anticholinergic activity. It is well tolerated and safe in overdosage. It can cause postural hypotension and priapism due to its α_1 blocking effects.

Nefazodone blocks serotonin reuptake and is an effective antidepressant. It is well tolerated-causes sedation and mild postural hypotension. Nefazodone is used in the prophylaxis of recurrent depression.

Venlafaxine is considered by some as atypical antidepressant because it inhibits the reuptake of noradrenaline in addition to 5 HT (Serotonin and noradrenaline reuptake inhibitor - SNRI). It is thought to be faster acting and may be useful in patients not responding to other antidepressants.

Mirtazapine blocks 5HT₂, 5HT₃ and α_2 receptors and enhances the release of NA and 5HT. It is faster acting - action starts by one week of treatment. It causes sedation but other side effects are negligible.

Bupropion is a weak DA reuptake inhibitor and has CNS stimulant effects. It is used in depression with anxiety. Bupropion is also used to help stop smoking (along with nicotine patch).

Mianserin acts by blocking presynaptic α_2 receptors but toxicity including blood dyscrasias, seizures and liver damage has limited its use.

Uses of Antidepressants

1. *Endogenous depression* Antidepressants are used over a long period. The response appears after 2-3 weeks of treatment. The choice of drug depends on the side effects and patient factors like age. In severe depression with suicidal tendencies, electroconvulsive therapy (ECT) is given.
2. *Panic attacks, Post-traumatic stress disorders* and other anxiety disorders—all respond to antidepressants (acute episodes of anxiety are known as panic attacks).
3. *Obsessive compulsive disorders* SSRIs and clomipramine are effective.
4. *Nocturnal enuresis* in children may be treated with antidepressants only when other measures fail and drugs are indicated.
5. *Psychosomatic disorders* Newer antidepressants are tried in fibromyalgia, irritable bowel syndrome, chronic fatigue, tics, migraine and sleep apnoea.
6. *Other indications* Attention deficit hyperactivity disorder, chronic pain and chronic alcoholism—may result in depression—antidepressants are tried.

MOOD STABILIZERS

Mood stabilizers control the mood swings that are seen in bipolar mood disorders.

Mood stabilizers include—

Lithium

Sodium valproate

Carbamazepine

Lamotrigine

Gabapentin

Lithium has been used for several decades but several antiepileptics like carbamazepine, valproic acid and gabapentin are now being tried.

Lithium is a monovalent cation. On prophylactic use in bipolar mood disorder (manic-depressive illness), lithium acts as a mood stabilizer. It prevents swings of mood and thus reduces both the depressive and manic phases of the illness. Given in acute mania, it gradually suppresses the episode over weeks.

Mechanism of action of lithium is complex and not fully understood. It is thought that lithium blocks the formation of inositol from IP_3 and thereby inhibits the regeneration of phosphatidyl inositol (PI). Depletion of membrane phosphatidyl inositol results in inhibition of receptor mediated effects through IP_3 and DAG. This is the accepted mechanism of action.

Pharmacokinetics Lithium is a small ion and mimics the role of sodium in excitable tissues. Given orally it is well-absorbed. It is filtered at the glomerulus but reabsorbed like sodium. Steady state concentration is reached in 5-6 days. Lithium is secreted in sweat, saliva and breast milk. Since safety margin is narrow, *plasma lithium concentration needs to be monitored* (0.5-1 mEq/lit is the therapeutic plasma concentration). 3-5 mEq/lit can cause fatal toxicity.

Adverse effects Lithium is a drug of low therapeutic index and side effects are common. Nausea, vomiting, mild diarrhoea, thirst and polyuria occur initially in most patients. Weight gain can also occur. As the plasma concentration rises, hypothyroidism, CNS effects like coarse tremors, drowsiness, giddiness, confusion, ataxia, blurred vision and nystagmus are seen. In severe overdose, delirium, muscle twitchings, convulsions, arrhythmias and renal failure develop.

Precautions

1. Minimum effective dose should be used.
2. Patients should always use the same formulation.

3. Patients should be made aware of the first symptom of toxicity.
4. Lithium is contraindicated in pregnancy.
4. Other uses – Lithium is tried in recurrent neuropsychiatric disorders, childhood mood disorders, hyperthyroidism and inappropriate ADH secretion syndrome.

Drug Interactions

1. Diuretics enhance sodium loss and lithium absorption from the kidney. This increases plasma lithium levels resulting in toxicity.
2. NSAIDs reduce lithium elimination and enhance toxicity.

Uses

1. Prophylaxis of bipolar mood disorder—episodes of mania and depression and their severity are reduced.
2. Acute mania – since the response to lithium is slow, neuroleptics are preferred.
3. Depression – Lithium is tried along with other antidepressants as an add-on drug in the treatment of severe recurrent depression.

Other Mood Stabilizers

Because of difficulty in using lithium, other drugs are being tried. The antiepileptics carbamazepine, sodium valproate and gabapentin are found to be useful, less toxic alternatives (see Chap 24).

Carbamazepine is found to be effective in preventing the relapses of bipolar mood disorder and in the treatment of acute mania. It can be combined with lithium for better therapeutic effects but lithium can enhance the toxicity of carbamazepine.

Sodium valproate can be tried alone in mild to moderate cases or along with lithium in refractory cases.

Lamotrigine, gabapentin and other newer antiepileptics are being tried in the prophylaxis of bipolar mood disorder as alternatives to lithium.

CNS Stimulants

Drugs that have a predominantly stimulant effect on the CNS may be broadly divided into:

1. *Respiratory stimulants*
Doxapram, nikethamide
2. *Psychomotor stimulants*
Amphetamine, cocaine
methylxanthines
3. *Convulsants*
Leptazol, strychnine.

Respiratory stimulants are also called *analeptics*. These drugs stimulate respiration and are sometimes used to treat respiratory failure. Though they may bring about temporary improvement in respiration, the mortality is not reduced. They have a low safety margin and may produce convulsions.

Doxapram appears to act mainly on the brainstem and spinal cord and increase the activity of respiratory and vasomotor centres.

Adverse effects are nausea, cough, restlessness, hypertension, tachycardia, arrhythmias and convulsions.

Uses

1. Doxapram is occasionally used IV as an analeptic in acute respiratory failure.
2. Apnoea in premature infants not responding to theophylline.

Nikethamide is not used because of the risk of convulsions.

Psychomotor stimulants Amphetamine and dextroamphetamine are sympathomimetic drugs (Chapter 11).

Cocaine is a CNS stimulant, produces euphoria and is a drug of abuse (Page 133).

Methylxanthines Caffeine, theophylline and theobromine are the naturally occurring xanthine alkaloids. The beverages—coffee contains caffeine; tea contains theophylline and caffeine; cocoa has caffeine and theobromine.

Actions

CNS Caffeine and theophylline are CNS stimulants. They bring about an increase in mental alertness, a reduction of fatigue, produce a sense of well being and improve motor activity and performance with a clearer flow of thought. Caffeine stimulates the respiratory centre. Higher doses produce irritability, nervousness, restlessness, insomnia, excitement and headache. High doses can result in convulsions.

CVS Methylxanthines increase the force of contraction of the myocardium and increase the heart rate and therefore increase the cardiac output. But, they also produce peripheral vasodilatation which tends to decrease the BP. The changes in BP are therefore not consistent. Caffeine causes vasoconstriction of cerebral blood vessels.

Kidneys The xanthines have a diuretic effect and thereby increase the urine output.

Smooth muscle Xanthines cause relaxation of smooth muscles especially the bronchial smooth muscle (Page 218).

Skeletal muscle Xanthines enhance the power of muscle contraction and thereby increase the capacity to do muscular work by both a central stimulant effect and the peripheral actions.

GI tract Xanthines increase the secretion of acid and pepsin in the stomach and are gastric irritants.

Adverse effects include nervousness, insomnia, tremors, tachycardia, hypotension, arrhythmias, headache, gastritis, nausea, vomiting, epigastric pain and diuresis. High doses produce convulsions. Tolerance develops after sometime. Habituation to caffeine is common.

Uses

- (i) *Headache* Because of the effect of caffeine on cerebral blood vessels, it is combined

with ergotamine for the relief of migraine headache. Caffeine is also combined with aspirin/paracetamol for the treatment of headache.

- (ii) *Bronchial asthma* Theophylline is used in the treatment of bronchial asthma.

NOOTROPICS

Nootropics are drugs that improve memory and cognition. They are also called cognition enhancers.

Piracetam – described as a ‘nootropic agent’ is thought to protect cerebral cortex from hypoxia and improve learning and memory. In higher doses it also inhibits platelet aggregation. Adverse effects include insomnia, weight-gain, nervousness, depression and gastrointestinal disturbances.

Piracetam has been tried in dementia, myoclonus, stroke and other cerebrovascular accidents; alcoholism, behavioural disorders and learning problems in children and in vertigo. The beneficial effects in all these are not proved.

Autacoids

Autacoids are substances formed in various tissues, have complex physiologic and pathologic actions and act locally at the site of synthesis. They have a brief action and are destroyed locally. Hence they are called 'local hormones' and differ from true hormones which are produced by specific cells and reach their target tissues through circulation. The word autacoid is derived from Greek: *autos* = self *akos* = remedy.

Autacoids Include (Fig. 31.1)

Histamine, 5-hydroxytryptamine
Angiotensin, kinins,
Prostaglandins, leukotrienes,
platelet activating factor.

HISTAMINE

Histamine or tissue amine (*Histos* = tissue) is a biogenic amine formed in many tissues. It is also found in the venoms of bees, wasps and other stinging secretions.

Synthesis, Storage, Distribution and Degradation

In humans, histamine is formed by the decarboxylation of the amino acid histidine. Large amounts are found in the lungs, skin and intestines. It is stored in the granules of the mast cells and basophils in an inactive form. Non-mast cell histamine found in brain,

serves as a neurotransmitter. Degranulation of the mast cells release histamine which is quickly degraded by deamination and methylation.

Mechanism of Action

Histamine produces its effects by acting on the histamine receptors. Three subtypes are known.

- H_1 —present in lungs, gut, blood vessels, nerve endings and brain.
- H_2 —stomach (gastric glands), heart, blood vessels and brain.
- H_3 —CNS.

Actions

1. CVS Histamine dilates small blood vessels resulting in hypotension accompanied by reflex tachycardia. Cerebral blood vessels dilate which causes severe throbbing headache.

Triple response Intradermal injection of histamine elicits triple response comprising of:

- (i) *red spot at the site* (flush) - due to local capillary dilation.
- (ii) *flare* - redness surrounding the 'flush' due to arteriolar dilatation.
- (iii) *wheel* - local oedema due to the escape of fluid from the capillaries.

This response is accompanied by pain and itching.

2. *Smooth muscle* Histamine causes contraction of the nonvascular smooth muscles.

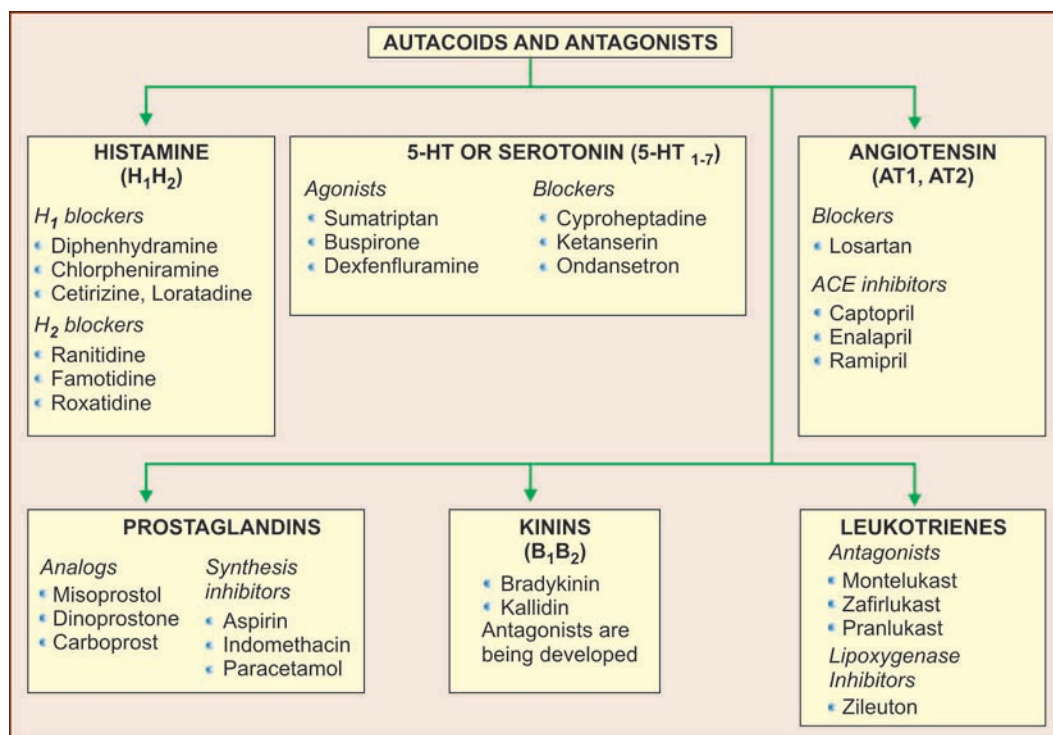


Fig. 31.1: Some autacoids with examples of agonists and antagonists, Receptor types are given in brackets

Thus bronchospasm and increased intestinal motility are produced.

Actions on other visceral smooth muscles like uterus are insignificant in humans.

3. *Glands* Histamine is a powerful stimulant of the gastric acid secretion—acts through H₂ receptors (see page 239). It also stimulates pepsin and intrinsic factor secretion.

4. *CNS* Histamine functions as a neurotransmitter in the CNS.

5. *Nerve endings* Histamine stimulates sensory nerve endings causing pain and itching.

Adverse reactions include hypotension, flushing, tachycardia, headache, wheal, bronchospasm and diarrhoea.

Uses

Histamine is of no therapeutic value. It is occasionally used in some diagnostic tests like.

1. *Testing gastric acid secretion* To test the acid secreting ability of the stomach. But now pentagastrin is preferred for this purpose.
2. *Diagnosis of pheochromocytoma* Histamine releases catecholamines and rises BP—now not used.
3. *Pulmonary function* To test for bronchial hyperreactivity.

Histamine Substitutes

Betazole is a H₂ agonist and can be used in gastric function tests. *Betahistine* is a H₁ agonist used to control vertigo in Meniere's disease.

ANTIHISTAMINES

Histamine antagonists can be H₁ receptor blockers and H₂ receptor blockers.

Drugs that competitively block H_1 histamine receptors are conventionally called the 'antihistamines'. H_2 blockers are used in the treatment of peptic ulcer Table 34.2 (Page 240).

Classification

Sedative

Diphenhydramine, dimenhydrinate, promethazine

Less sedative

Pheniramine, chlorpheniramine, cyclizine, meclizine, buclizine, mepyramine, tripeleennamine.

Newer non-sedative (II generation agents)

Terfenadine, astemizole, loratadine, cetirizine, fexofenadine, acrivastine, azelastine, mizolastine, levocabastine, mequitazine

Actions

1. *Blockade of actions of histamine* H_1 receptor antagonists block the actions of histamine on H_1 receptors. They block the histamine induced effects on smooth muscles of the gut, bronchi, blood vessels and triple response.
2. *Sedation* Antihistamines cause CNS depression; sedation, dizziness, inability to concentrate and disturbances of coordination are common. Alcohol and other CNS depressants potentiate this action. Some patients may experience CNS stimulation resulting in tremors, restlessness and insomnia.
3. *Antimotion sickness effects* Several antihistamines prevent motion sickness and vomiting due to other labyrinthine disturbances. Some of them also control vomiting of pregnancy.
4. *Antiparkinsonian effects* Some of them suppress tremors, rigidity and sialorrhoea probably due to their anticholinergic properties.

5. *Anticholinergic actions* Many of the H_1 blockers have anticholinergic property. This accounts for both useful and adverse effects. Such antihistamines have antisecretory, antiemetic and antiparkinsonian effects.

6. *Other actions* Antihistamines also have local anaesthetic effects in high doses. Some of them also block α_1 adrenergic and 5-HT receptors.

Pharmacokinetics Antihistamines are well-absorbed, widely distributed in the body, metabolised in the liver and are excreted in the urine. Dose and route of administration are given in Table 31.1.

Adverse reactions are mild and on continued use tolerance develops.

Sedation, dizziness, motor incoordination and inability to concentrate make driving dangerous while on antihistamines. Anticholinergic effects like dryness of mouth, blurred vision, constipation and urinary retention may be troublesome. Epigastric distress, allergic reactions and headache can also occur. Many of them are teratogenic.

Newer non-sedative antihistamines also called II generation antihistamines have the following advantages (Table 31.2) over classical antihistamines:

- No sedation because they poorly cross the blood-brain barrier.
- No anticholinergic side effects as they are pure H_1 blockers and do not block cholinergic receptors.
- Some of them like astemizole are long-acting.

However, the therapeutic indications of these agents are limited to allergic disorders like allergic rhinitis and chronic urticaria. They are more expensive. Terfenadine and astemizole can sometimes cause *torsades de pointes* and fatal ventricular arrhythmias; erythromycin, ketoconazole and itraconazole

Table 31.1: Dose and preparations of some antihistamines

Antihistamine	Dose and route	Trade name
Diphenhydramine HCl	25-50 mg oral IM 10 mg	BENADRYL Cap, Syr
Dimenhydrinate	25-50 mg oral, IM	DRAMAMINE Tab, Syr Inj
Promethazine	25-50 mg oral, IM	PHENERGAN Tab, Syr, Inj
Promethazine chlorotheophyllinate	25-75 mg oral	AVOMINE Tab
Pheniramine maleate	25-50 mg oral, IM	AVIL Tab, Syr, Inj
Chlorpheniramine	4-20 mg oral, IM	ZEET Tab, Syr, Inj
Cyclizine HCl	50 mg oral	MAREZINE Tab
Meclizine HCl	25-50 mg oral	ANCOLAN Tab
Bucizine	25-50 mg oral	LONGIFENE Tab, Syr
Cinnarizine	25-50 mg oral	STUGERON Tab
<i>Nonsedative antihistamines</i>		
Loratadine	10 mg oral	LORFAST, Tab, Syr
Cetirizine	10 mg oral	ALERID, Tab, Syr
Azelastine	8 mg oral	SEMPRAX, Tab

potentiate this cardiotoxicity. Terfenadine and astemizole are therefore withdrawn now. Loratadine and fexofenadine appear to be free from the cardiotoxic effect. Though considered nonsedative, cetirizine can cause some sedation when compared to other second generation agents.

Other Drugs

Doxepine-A tricyclic antidepressant also blocks H_1 receptors. Hydroxyzine is a good antipruritic and has a long duration of action- it is used in skin allergies- but it causes significant sedation. Cyproheptadine blocks both H_1 histamine and $5HT_2$ serotonin receptors.

Uses

1. *Allergic reactions* Antihistamines are useful for the prevention and treatment of symptoms of allergic reactions. They are effective in allergic rhinitis, conjunctivitis, hayfever, urticaria, pruritus, some allergic skin rashes and pollinosis.
2. *Common cold* Antihistamines reduce rhinorrhoea and afford symptomatic relief in common cold.
3. *Motion sickness* Given 30-60 minutes before journey, antihistamines prevent motion sickness - promethazine, dimenhydrinate, meclizine and cyclizine are useful. They are also useful in treating vertigo of Meniere's disease and other vestibular disturbances- dimenhydrinate, meclizine and cinnarizine are preferred.
4. *Antiemetic* Promethazine is used to prevent drug induced and postoperative vomiting. It has also been used in 'morning sickness.'
5. *Preanaesthetic medication* For the sedative, anticholinergic and antiemetic properties,

Though they prevent bronchospasm induced by histamine, antihistamines are *not* useful in bronchial asthma because many other mediators are also involved in the pathogenesis of bronchial asthma. Moreover antihistamines render the respiratory secretions thicker making it difficult to cough it out.

promethazine has been used as pre-anaesthetic medication.

6. *Hypnotic* The sedative antihistamines are sometimes used to induce sleep. Hydroxyzine has been used as an anxiolytic.
7. *Parkinsonism* Some of them are useful in drug induced parkinsonism due to their anticholinergic action.
8. *Cough* due to postnasal drip can be controlled by antihistamines like diphenhydramine.

5-HYDROXYTRYPTAMINE

5-Hydroxytryptamine (serotonin, 5-HT) was isolated in 1948 and has been of great pharmacological interest. It is found in various plant and animal tissues.

In human body, 5-HT is present in the intestines, platelets and brain. It is synthesized from the amino acid tryptophan and is stored in granules. It is degraded mainly by MAO.

5-HT receptors The actions of serotonin are mediated through its receptors. Seven types of 5-HT receptors (5-HT₁₋₇) with further subtypes of 5-HT₁, 5-HT₂ and 5-HT₅ receptors are presently known. Many receptor-selective agonists and antagonists are being developed.

Actions

1. **CVS** The action on blood vessels is complex. Large vessels are constricted

while arterioles dilate. A characteristic triphasic response is seen on blood pressure following IV injection.

- Initial fall in BP is due to increased vagal activity
 - Rise in BP—due to vasoconstriction of large vessels, followed by
 - fall in BP—due to arteriolar dilation.
2. *GI tract* Increases GI motility and contraction resulting in diarrhoea.
 3. *Other actions* Weak bronchoconstriction, platelet aggregation; stimulation of sensory nerve endings — causes pain if injected into the skin. 5-HT is a neurotransmitter in the CNS.

Physiological and pathophysiological role 5-HT is postulated to be having a role in peristalsis, vomiting, platelet aggregation, homeostasis and inflammation. It is also thought to initiate the vasoconstriction in migraine.

Drugs acting on 5-HT receptors Serotonin has no therapeutic uses. However its receptor agonists and antagonists have been used in various conditions (Table 31.3).

Serotonin Agonists

Sumatriptan— a 5-HT_{1D} agonist is effective in the treatment of acute migraine and cluster headache. Given orally/SC at the onset of an attack, sumatriptan relieves headache and also suppresses nausea and vomiting of migraine. It is short-acting.

Adverse effects include dizziness, altered sensations, weakness, chest discomfort and

Table 31.2: Compare and contrast diphenhydramine and loratadine

Features	Diphenhydramine	Loratadine
1. Receptors blocked	H ₁ histamine, M ₁ muscarinic	H ₁ selective
2. t _{1/2}	4–6 hrs	16–18 hrs
3. Ability to cross BBB	Present	Absent
4. Sedation	Yes	No
5. Anticholinergic effects	Yes	No
6. In rhinorrhoea	Useful	Not useful
7. Route of administration	Oral and Parenteral	Oral

neck pain. It is contraindicated in coronary artery disease.

Other Agonists

- *Buspirone* (Page 194) is a 5-HT_{1A} agonist-antagonist used as an antianxiety agent.
- *Dexfenfluramine* (Page 75) is used as an appetite suppressant.

Serotonin Antagonists

- *Cyproheptadine* blocks 5-HT₂, H₁ histamine and cholinergic receptors. It increases appetite and is used to promote weight gain especially in children. It is also used in carcinoid tumours.
- *Ketanserin* blocks 5-HT₂ receptors and antagonises vasoconstriction and platelet aggregation promoted by 5-HT. It is used in hypertension.
- *Ondansetron* is a 5-HT₃ antagonist (see page 245) used in the prevention and treatment of vomiting.

Many other drugs including some antihistamines also block serotonin receptors.

Ergot Alkaloids

Ergot alkaloids are produced by *Claviceps purpurea*, a fungus that infects rye, millet and other grains. Consumption of such grains results in 'ergotism' manifested as gangrene of the hands and feet, hallucinations and other CNS effects. Barger and Dale isolated ergot alkaloids in 1906.

Natural ergot alkaloids include ergometrine, ergotamine and ergotoxine. The semisynthetic derivatives are also available.

Actions

Ergot alkaloids have agonist, partial agonist and antagonistic actions at 5-HT and alpha adrenergic receptors and agonistic actions at CNS dopamine receptors. Thus their actions

are complex. Some of them are powerful hallucinogens, e.g. lysergic acid diethylamide (LSD). They cause stimulation of smooth muscles—some stimulate mainly vascular smooth muscles and others mainly uterine smooth muscles. The vasoconstrictor effect is responsible for gangrene.

Adverse effects like nausea, vomiting and diarrhoea are common. Prolonged use results in gangrene due to persistent vasospasm.

Uses

1. Migraine
2. Postpartum haemorrhage—ergometrine is used for prevention and treatment

Drugs Used in the Treatment of Migraine

Migraine is a common disorder characterised by severe, throbbing, unilateral, headache often associated with nausea, vomiting and fatigue lasting for several hours. In the classical migraine, a brief 'aura' of visual disturbances occurs prior to the headache. An attack is triggered by factors like stress, anxiety, excitement, food (like chocolate and cheese) and hormonal changes. These triggering factors stimulate the release of vasoactive substances from nerve endings which are responsible for the events that follow. However the exact pathophysiology is not understood and several hypotheses have been put forward.

Drugs Used in Acute Attacks

Drugs should be taken at the initiation of attack.

- Aspirin, paracetamol or other NSAIDs are effective.
- Metoclopramide can be combined with aspirin as it is an antiemetic and also speeds up absorption of aspirin.

Table 31.3: Serotonin agonists, antagonists and their therapeutic uses

	Receptor	Uses	Comments
<i>Agonists</i>			
Sumatriptan	5-HT _{1D}	• Acute migraine • Cluster headache	Short-acting; may need repetition of dose
Buspirone	5-HT _{1A} (Agonist-antagonist)	Anxiolytic	—
Dexfenfluramine	5-HT	Appetite suppressant	Patients should be carefully monitored for risk of pulmonary hypertension
<i>Antagonists</i>			
Cyproheptadine	5-HT ₂ ; H ₁ -histamine and muscarinic receptors	• Appetite stimulant • Carcinoid tumours	—
Ketanserin	5-HT ₁ and 5-HT ₂	Hypertension	Also antagonises platelet aggregation promoted by 5-HT
Ondansetron	5-HT ₃	Antiemetic	—
<i>Ergot alkaloids</i>			
Ergotamine	5-HT ₁ partial agonist/antagonist	Acute attack of migraine	—
Ergometrine	5-HT ₁ partial agonist/antagonist	Postpartum haemorrhage	—
Methysergide	5-HT ₂ partial agonist/antagonist	Prophylaxis of migraine	Not preferred due to risk of retroperitoneal and mediastinal fibrosis

- Ergotamine given orally (or sublingual/rectal when vomiting is present) is an effective alternative.
- Sumatriptan is very effective but short-acting.

Prophylaxis

When the attacks are frequent and severe, prophylaxis is needed. Drugs used for the prophylaxis are:

- *β-adrenergic blockers* Propranolol reduces frequency and severity of attacks. The initial dose is 40 mg twice daily and is gradually increased to a maximum of 160 mg twice daily. The mechanism of action is not exactly known.
- *Ca⁺⁺ channel blockers* Flunarizine may be useful. It has weak Ca⁺ channel blocking properties and is thought to be selective for the CNS. Adverse effects include hypotension, flushing, drymouth, constipation and sedation.
- *Pizotifen and cyproheptadine* block 5-HT and H₁ histamine receptors; may be used as alternatives.
- *Tricyclic antidepressants* Amitriptyline may be tried but it is associated with many adverse effects, (see page. 195)

- *Methysergide* blocks 5-HT receptors but due to adverse effects like retroperitoneal fibrosis, it is not preferred.

EICOSANOIDS

Eicosanoids are 20-carbon (eicosa referring to the 20-carbon atoms) unsaturated fatty acids derived mainly from arachidonic acid in the cell walls. The principal eicosanoids are the prostaglandins (PG), the thromboxanes (TX), and the leukotrienes (LT).

Biosynthesis

Eicosanoids are synthesized locally in most tissues from arachidonic acid. The pathway for synthesis is shown in Figure. 31.2.

The cyclo-oxygenase (COX) pathway generates PGs and TXs while lipoxygenase (LOX) pathway generates LTs. There are 2 cyclo-oxygenase isozymes *viz.* COX-1 and COX-2. COX-1 is present in almost all cells and prostanoids (PGs and TXs) obtained from COX-1 mainly take part in physiological functions. COX-2 is induced by inflammation in the inflammatory cells and the prostanoids produced by COX-2 are

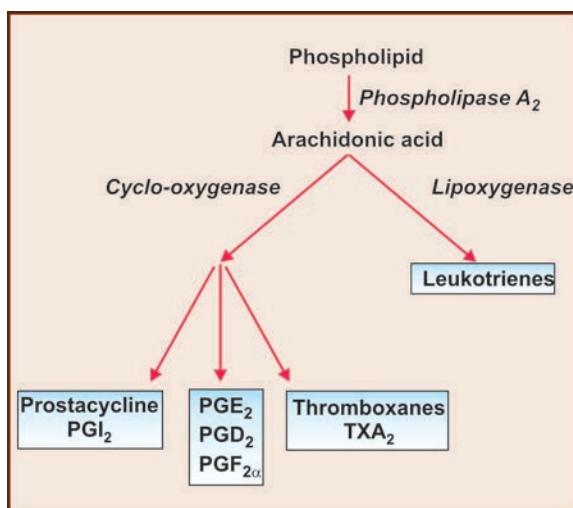


Fig. 31.2: Biosynthesis of eicosanoids

involved in inflammatory and pathological changes. All products of COX pathway are metabolised by oxidation and excreted in urine.

PROSTAGLANDINS AND THROMBOXANES

In 1930s it was found that human semen contains a substance that contracts uterine smooth muscle. As this substance was thought to originate in the prostate, they called it 'Prostaglandin' but it was later found to be produced in many tissues.

Prostanoid receptors

The prostanoids bring about their effects by acting on prostanoid receptors, which are G-protein coupled receptors. There are five classes of prostanoid receptors. They are-

- DP (for PGD₂)
- EP (for PGE₂)
- FP (for PGF_{2α})
- IP (for PGI₂)
- TP (for TXA₂)

Actions

The prostanoids act on many tissues to bring about the following effects.

1. CVS Prostacyclin causes vasodilation while TXA₂ causes vasoconstriction. PGE₂ and PGF_{2α} are weak cardiac stimulants.
2. GIT Most PGs and TXs stimulate gastrointestinal smooth muscle resulting in colic and watery diarrhoea. PGE₂ inhibits gastric acid secretion and enhances mucous production. Thus they have a protective effect on gastric mucosa.
3. Airways PGE₂ and PGI₂ relax bronchial smooth muscles while TXA₂ and PGF_{2α} contract them. They may have a role in the pathophysiology of bronchial asthma.
4. Platelets TXA₂ induces platelet aggregation while PGI₂ inhibits platelet aggregation.
5. Uterus PGE₂ and PGF_{2α} contract human uterus which is more sensitive to PGs

Prostaglandins

- 20-carbon unsaturated fatty acids synthesized from arachidonic acid through cyclo-oxygenase pathway
- Prostacycline (PGI_2) causes vasodilation while TXA_2 causes vasoconstriction
- PGs contract g.i. and bronchial (TXA_2 , PGE_2) smooth muscles. TXA_2 induces platelet aggregation (PGI_2 inhibits); PGE_2 and $\text{PGF}_{2\alpha}$ contract uterus. PGs stimulate bone turnover and sensitize the nerve endings to pain
- *Uses* Abortion, facilitation of labour, cervical priming, to control post-partum haemorrhage, to maintain the patency of ductus arteriosus, for prevention of platelet aggregation, open angle glaucoma and peptic ulcer.

during pregnancy. They also soften the cervix. Thus PGs may be involved in the initiation and progression of labour. PGs are produced by foetal tissues during labour. PGs present in the semen may facilitate movement of sperms and fertilization by coordinating the movement of the uterus. They also play a role in dysmenorrhoea and menorrhagia.

6. *Kidneys* PGE_2 and PGI_2 cause renal vasodilation and have a diuretic effect.
7. *CNS* PGs increase body temperature when administered into cerebral ventricles. They also induce sleep.
8. *Nerves* PGs sensitize sensory nerve endings to pain and on intradermal injection cause pain. They have a role in the genesis of inflammation.
9. *Bone* PGs stimulate bone resorption and formation-increase bone turnover.
10. Some PGs lower intraocular pressure.

Adverse effects depend on the type of PG, dose and route. Diarrhoea, nausea, vomiting,

fever, hypotension and pain due to uterine contractions are common.

PG analogs used therapeutically

Misoprostol	PGE_1
Gemeprost	PGE_1
Rioprostil	PGE_1
Alprostadil	PGE_1
Enprostil	PGE_2
Dinoprostone	PGE_2
Carboprost	15-Methyl $\text{PGF}_{2\alpha}$
Latanoprost	$\text{PGF}_{2\alpha}$
Dinoprost	$\text{PGF}_{2\alpha}$
Epoprostenol	PGI_2

*Uses*1. *Gynaecological and obstetrical*

- a. *Abortion* For I and II trimester abortion and ripening of cervix during abortion, PGE_2 and $\text{PGF}_{2\alpha}$ are used. They are also used with mifepristone to ensure complete expulsion of the products of conception.
- b. *Facilitation of labour* As alternative to oxytocics in patients with renal failure.
- c. *Cervical priming* Intravaginal PGE_2 is used.
- d. *Postpartum haemorrhage* Intramuscular $\text{PGF}_{2\alpha}$ is used as an alternative to ergometrine.

2. *Gastrointestinal*

Peptic ulcer PGE_1 (misoprostol) and PGE_2 (enprostil) are used for the prevention of peptic ulcer in patients on high dose NSAIDs.

3. *Cardiovascular*

- a. *Patent ductus arteriosus* Patency of foetal ductus arteriosus depends on local PG synthesis. In neonates with some congenital heart diseases, patency of the ductus arteriosus is maintained with PGs until surgery is done.
- b. To prevent platelet aggregation during haemodialysis.

4. *Other uses* PGs are used in pulmonary hypertension and some peripheral vascular diseases. They can also be used in open angle glaucoma to lower intraocular pressure.

OTHER AUTACOIDS

LEUKOTRIENES

Leukotrienes (LT) are products of arachidonic acid metabolism synthesized by the lipoxygenase pathway and are found in the lungs, platelets, mast cells and white blood cells ('Leuko'—because they are found in white cells; 'trienes'—they contain triene system of double bonds). LTA_4 is the precursor from which LTB_4 , LTC_4 , LTD_4 , LTE_4 and LTF_4 are derived. LTC_4 , LTD_4 and LTE_4 are together known as slow reacting substances (SRS-A) of anaphylaxis. The LTs produce their effects through specific receptors.

Actions

Leukotrienes cause vasoconstriction, increase vascular permeability leading to oedema, increase airway mucous secretion and are potent bronchiolar spasmogens. Given subcutaneously they cause wheal and flare. Leukotrienes have a role in inflammation including rheumatoid arthritis, psoriasis and ulcerative colitis. They also contribute to bronchial hyper-responsiveness in bronchial asthma.

Drugs like zileuton that inhibit lipoxygenase and thereby block the synthesis of leukotrienes are useful in the treatment of bronchial asthma and allergic rhinitis.

Leukotriene Receptor Antagonists

Montelukast, zafirlukast and pranlukast block the actions of LTC_4 and LTD_4 on the bronchial and vascular smooth muscles. They are useful

as adjuvants in bronchial asthma. They are all effective orally.

PLATELET ACTIVATING FACTOR (PAF)

PAF is an important mediator in acute and chronic, allergic and inflammatory phenomena. PAF is released from inflammatory cells on stimulation and acts on specific receptors. It causes local vasodilatation resulting in oedema, hyperalgesia and wheal formation. It is a potent chemotaxin for leucocytes and a spasmogen on bronchial and intestinal smooth muscles. It is a mediator of inflammation.

ANGIOTENSIN

Angiotensins are peptides synthesized from the precursor angiotensinogen. Angiotensinogen, a circulating protein synthesized in the liver is converted sequentially to angiotensin I, angiotensin II and angiotensin III (Fig. 31.2). Angiotensin converting enzyme is widely distributed in the body. It is present in blood vessels, kidneys, heart, brain, lungs, adrenals and other tissues. Angiotensin II, the most potent angiotensin acts through angiotensin receptors (AT_1 and AT_2) present on the tissues.

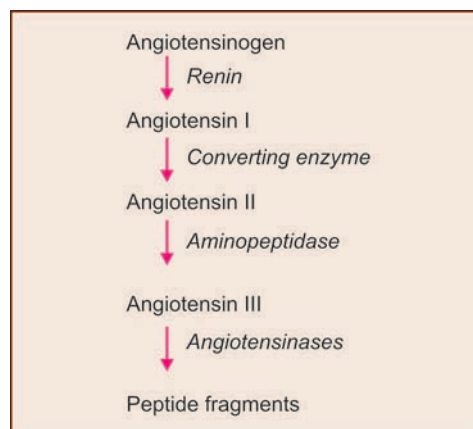


Fig. 31.3: Synthesis and metabolism of angiotensins

Actions

Angiotensin II causes vasoconstriction resulting in increased blood pressure. It stimulates the synthesis of aldosterone by the adrenal cortex, increases sodium reabsorption by the kidneys and increases the secretion of vasopressin. Angiotensin II also promotes the growth of vascular and cardiac muscle cells and may play a role in the development of cardiac hypertrophy as in hypertension. By these actions, renin-angiotensin system regulates the fluid and electrolyte balance as well as blood pressure.

Inhibitors of ACE and blockers of angiotensin II receptors are now used in the treatment of hypertension, congestive heart failure and other conditions that are due to excess of angiotensin II activity (see Section 4).

KININS

Kinins are vasodilator peptides formed from the precursor kininogen by the action of the enzymes called kallikreins. Kallikreins are present in the plasma, kidneys, pancreas, intestines, salivary glands and other tissues. Bradykinin is the chief kinin.

Kinins are rapidly degraded by kininase II which is same as ACE and has a very short $t_{1/2}$ (< 15 seconds).

Actions

Kinins are potent vasodilators and cause a brief fall in BP. They stimulate contraction of other smooth muscles — thus they induce bronchospasm in asthmatics, slow contraction of intestines (*Brady*= *slow*) and uterus. Kinins mediate inflammation, and stimulate the pain nerve endings. Kinins produce their actions by acting through B_1 and B_2 receptors.

Drugs affecting the kallikrein-kinin system— B_1 and B_2 antagonists are now being developed.

CYTOKINES

Cytokines are also considered as autacoids. They are peptides released from the inflammatory cells. They are classified into 5 families.

- Interleukins
- Colony stimulating factors
- Chemokines
- Growth factor and tumour necrosis factors
- Interferons

Cytokines stimulate specific receptors to bring about their effects. IL-1 and TNF - α are involved in inflammation - they are pro-inflammatory cytokines while IL-4, IL-10 and IL-13 inhibit inflammatory activity - they are anti-inflammatory cytokines. The interferons α and β have antiviral activity while interferon γ has immunoregulatory activity and is used in multiple sclerosis.

Section 7

Respiratory System

32

Drugs Acting on Respiratory System

DRUGS USED IN THE TREATMENT OF BRONCHIAL ASTHMA

Bronchial asthma is characterised by dyspnoea and wheeze due to increased resistance to the flow of air through the bronchi. Bronchospasm, mucosal congestion and oedema result in increased resistance. The tracheobronchial smooth muscle is hyper-responsive to various stimuli like dust, allergens, cold air, infection and drugs. These trigger-factors trigger an acute attack.

Antigen-antibody interaction on the surface of mast cells cause (Fig. 32.1):

- (i) degranulation of mast cells releasing stored mediators of inflammation
- (ii) synthesis of other inflammatory mediators which are responsible for bronchospasm, mucosal congestion and oedema.

Inflammation is the primary pathology.

Clinically 2 types of asthma are identified.

- (a) *Extrinsic asthma* Starts at an early age, occurs in episodes; the patient has a family history of allergies.
- (b) *Intrinsic asthma* Starts in the middle age and assumes chronic form. There is no family history of allergies.

Drugs used in the bronchial asthma may be grouped as follows.

CLASSIFICATION

1. Bronchodilators
 - a. *Sympathomimetics*
 - i. Selective β_2 agonists
 - Short acting-*
 - Salbutamol, terbutaline.
 - Longer acting -*
 - Salmeterol, fenoterol, formoterol, pirbuterol, Ibusterol
 - ii. Nonselective agents
 - Adrenaline, isoprenaline, ephedrine.
 - b. *Methylxanthines* -
Theophylline, aminophylline.
 - c. *Anticholinergics* -
Ipratropium bromide, atropine.
2. Anti-inflammatory agents
 - a. *Systemic* - Glucocorticoids
Hydrocortisone, Prednisolone.
 - b. *Inhalational* -
Beclomethasone, Budesonide, Flunisolide, Triamcinolone
3. Mast cell stabilizers -
Disodium cromoglycate, Nedocromil, Ketotifen.
4. Leukotriene receptor antagonists -
Montelukast, zafirlukast.

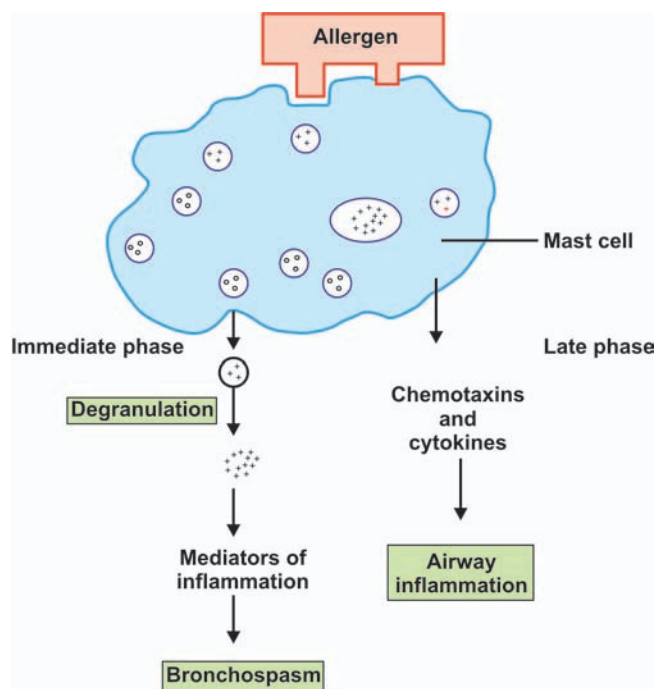


Fig. 32.1: Immediate and late responses of mast cell activation by antigen

SYMPATHOMIMETIC DRUGS

Sympathomimetics (see Chapter 11) are potent bronchodilators and are the most useful drugs to relieve bronchospasm.

Mechanism of action Adrenergic agonists stimulate β_2 receptors in the bronchial smooth muscles which in turn cause activation of adenylyl cyclase resulting in increased cAMP levels (Fig. 32.2). This increased cAMP leads to bronchodilatation. The increased cAMP in mast cells inhibits the release of inflammatory mediators. They also reduce bronchial secretions and congestion (by acting on α receptors).

Short Acting β_2 Agonists like salbutamol (albuterol) and terbutaline are given by inhalation, they are fastest acting bronchodilators with peak effect in 10 minutes. The action lasts for 6 hours. Adverse effects to β_2 agonists include muscle tremors, palpitation and nervousness.

Selective β_2 agonists are the most commonly used bronchodilators as they are the most effective, fast-acting, convenient and relatively safe bronchodilators. They are available as metered dose inhalers, nebulizers, injections and also tablets for oral use. The proper technique in using the inhaler should be taught. 'Spacers' (Fig. 32.3) can be used in children and adults who cannot follow the right technique of inhalation.

Oral β_2 agonists have higher adverse effects than inhaled ones and are used only in small children who cannot use inhalers and have occasional wheezing (1-4 mg 6 hourly).

Longer Acting β_2 Agonists like salmeterol have a slow onset of action (hence not useful in acute attacks) but the effect remains for 12 hours. Salmeterol is therefore used for long-term maintenance and for prevention of nocturnal asthmatic attacks.

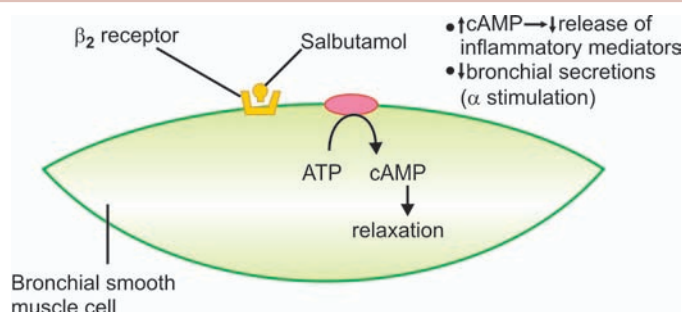


Fig 32.2: Mechanism of action of β_2 agonists in bronchial asthma

Other longer acting agents are also available for use - they are *formoterol*, *fenoterol*, *bambuterol* and *pirbuterol*.

The long term use of β_2 agonists may result in reduced response due to development of tolerance. Management of acute bronchospasm becomes a problem in such patients.

Others include adrenaline, ephedrine and isoprenaline. Though these produce prompt bronchodilation, they are not preferred due to the risk of adverse effects.

Bronchodilation by ephedrine is slow in onset. Because of low efficacy, side effects and availability of better drugs, ephedrine is not preferred.

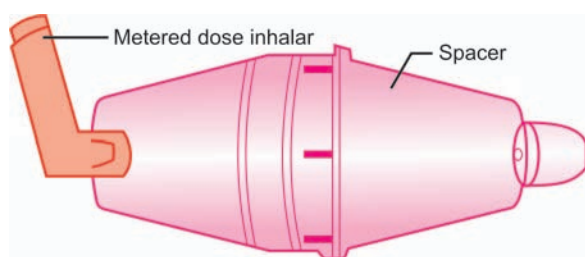


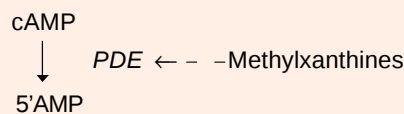
Fig 32.3: Spacer

METHYLYXANTHINES (Page 203)

Theophylline and its derivatives like *aminophylline* are good bronchodilators.

Mechanism of action Phosphodiesterase (PDE) is the enzyme that degrades cyclic AMP.

Methylxanthines inhibit PDE and thereby enhance cAMP levels which brings about bronchodilation. cAMP also inhibits the release of mediators of inflammation.



Aminophylline is given intravenously, **slowly**, in acute attacks of asthma not responding to β_2 agonists. In an acute attack, drugs given by inhalation may sometimes fail to reach the bronchioles because of severe bronchospasm. Intravenous aminophylline may then be tried. 250 mg aminophylline should be injected slow IV over 15-20 minutes. Rapid IV injection may cause collapse and death due to hypotension and arrhythmias. Convulsions can also occur and should be carefully watched for.

Adverse effects Theophylline is a drug of low therapeutic index. Gastric irritation, vomiting, insomnia, tremors, diuresis, palpitation, and hypotension are quite common. Higher doses cause restlessness, delirium, convulsions and arrhythmias. Children may develop behavioural abnormalities on prolonged use—should be avoided.

Status in bronchial asthma Theophylline is a second line drug in bronchial asthma.

1. *Chronic asthma* Oral theophylline can be used to control mild to moderate asthma. Etophylline + 80% theophylline (Deriphylline) injections (IM) are used to relieve acute attacks. When used over a long-term, plasma levels should be monitored.
2. *Acute severe asthma (status asthmaticus)* Intravenous aminophylline is tried when sympathomimetics fail to relieve bronchospasm—but is found to be less effective.

ANTICHOLINERGICS

Anticholinergics (See chap. 8) relax bronchial smooth muscles but response is slower than sympathomimetics. *Ipratropium bromide* is given by inhalation and its actions are largely confined to the respiratory tract. It is more effective in chronic bronchitis including chronic obstructive pulmonary disease (COPD). It is safe and well-tolerated. Unlike atropine it does not dry up the secretions and hence does not inhibit mucociliary motility. Infact it may increase mucociliary clearance.

Uses

1. As an adjunct to β_2 agonists particularly in severe acute episodes.
2. As a bronchodilator in some cases of chronic bronchitis and COPD.

ANTI-INFLAMMATORY DRUGS

Glucocorticoids Since inflammation is the primary pathology in bronchial asthma, antiinflammatory agents afford significant benefit (See chap. 54).

Mechanism of action Steroids are not bronchodilators. They suppress the inflammatory response to antigen-antibody reaction and thereby reduce mucosal oedema and hyperirritability. They bind to steroid

receptors in the cytoplasm, drug receptor complex moves to the nucleus, binds to DNA and induces the synthesis of specific mRNA. This in turn results in the synthesis of specific proteins to bring about the following effects (Fig. 54.2, Page 349)

1. they decrease the formation of cytokines.
2. ↓ PG synthesis.
3. inhibit the production of leukotrienes and platelet activating factor.
4. reduce the influx of eosinophils into the lungs and thus reduce the release of mediators from them.
5. ↓ synthesis of interleukins.
6. restore response to β_2 agonist -(if tolerance has developed)-by upregulating β_2 receptors.

Glucocorticoids may be given systemically in acute episodes. Oral prednisolone is commonly used (dose 30-60 mg/day). The onset of response requires about 12 hours. Chronic asthma requires prophylaxis with inhaled steroids.

Inhaled steroids The use of inhalational steroids largely minimizes the adverse effects of steroids because of the small dose required, but they are not effective in acute attacks and are only of prophylactic value. They prevent episodes of acute asthma, reduce bronchial hyperreactivity and effectively control symptoms. The effect gradually develops after 1 week of treatment.

Side effects of inhaled steroids include hoarseness of voice - (by a direct effect on vocal cords), sore throat and oropharyngeal candidiasis. Rinsing the mouth and throat with water after each use can reduce the incidence of candidiasis and sore throat. HPA axis suppression is generally not seen in the recommended doses. But, the drug that is swallowed may be systemically absorbed. Large doses given for a long time may occasionally result in systemic effects of

steroids particularly in children. The use of a 'spacer' reduces this risk and the adverse effects are also less common when a spacer is used (Fig. 32.3).

Beclomethasone dipropionate, budesonide, triamcinolone and fluticasone are used as inhalers.

Beclomethasone dipropionate is available as metered dose inhaler and rotacaps. It is also available in combination with salbutamol.

Budesonide has the advantage of having high topical activity and the absorbed portion is rapidly metabolised (*Flunisolide* is available as nasal spray for allergic rhinitis.)

Fluticasone is poorly absorbed from the gut and also undergoes high first pass metabolism. Hence even when swallowed, systemic adverse effects are unlikely with fluticasone.

Status of Glucocorticoids in Asthma

1. *Acute exacerbation* A short course (5-7 days) of oral prednisolone 30-60 mg/day for 7 days is given in addition to β_2 agonists.
2. *Chronic asthma* Steroid inhalation (2-4 times a day) for a long period as prophylaxis.
3. *Status asthmaticus* Intravenous hydrocortisone hemisuccinate (100-200 mg) followed by oral prednisolone.

MAST CELL STABILIZERS

Cromolyn sodium (disodium cromoglycate) was synthesized in 1965.

Mechanism of Action

- Cromolyn inhibits the degranulation of mast cells and thereby inhibits the release of mediators of inflammation, particularly histamine.
- It also inhibits the release of cytokines.
- It may depress the neuronal reflexes which are exaggerated. But the exact mechanism of action is not known.

We know that cromolyn prevents bronchospasm and inflammation following exposure to allergen and decreases bronchial hyper-reactivity. It is therefore used for *prophylaxis*. It is *not* a bronchodilator - hence *not* useful in acute episodes.

Cromolyn sodium is used as an inhaler; it takes 2-4 weeks of treatment for the beneficial effects to develop. All patients do not respond but it should be tried in all suitable patients. Children are more likely to respond.

Adverse effects are rare. Throat irritation, cough and sometimes bronchospasm can occur on inhalation due to deposition of the fine powder. Allergic reactions are rare.

Uses

1. *Prophylaxis of bronchial asthma*—cromolyn sodium used over a long period—2 puffs—3-4 times daily reduces episodes of acute asthma. Young patients with extrinsic asthma are more likely to be benefitted. Cromolyn can also be used for prophylaxis before exposure to a known allergen.
2. *Allergic rhinitis*—Prophylactic nasal spray is used.
3. *Allergic conjunctivitis*—Eyedrops are used prophylactically- 1-2 drops, 3-4 times a day.

Preparations: FINTAL inhaler (1 mg), eyedrops 2%, nasal spray 2%, CROMAL inhaler 200 mg, eyedrops, nasal spray.

Nedocromil is similar to cromolyn sodium in its actions and uses. It is given twice daily.

Ketotifen is an antihistaminic with actions like cromolyn sodium. It inhibits airway inflammation but it is not a bronchodilator. It is given orally. Beneficial effects are seen after 6-12 weeks of use. It is used for the prophylaxis of bronchial asthma and other allergic disorders like allergic rhinitis, atopic dermatitis, urticaria and conjunctivitis.

Drowsiness and dry mouth are common side effects. It can also cause dizziness and weight gain.

LEUKOTRIENE RECEPTOR ANTAGONISTS

Leukotrienes are one of the important mediators of inflammation. They bring about bronchospasm, mucosal oedema, increase the influx of inflammatory cells and mucous production, by their actions on leukotriene receptors. **Zafirlukast, montelukast and pranlukast** are highly selective and competitive antagonists of leukotriene receptors. They block the effects of leukotrienes and thereby reduce mucosal oedema and relieve bronchospasm. They decrease the response to allergens. They inhibit exercise-induced and aspirin-induced bronchospasm. Adverse effects are rare - headache, rashes and gastrointestinal disturbances.

Montelukast and zafirlukast can be used in the prophylaxis of mild to moderate asthma as alternatives or as add-on drugs. They also reduce the dose of the steroid required. Bronchodilator effect is additive with β_2 agonists. Their place in asthma is yet to be clearly known.

Zileuton inhibits leukotriene synthesis by inhibiting the enzyme lipoxygenase. But it causes a rise in liver enzymes. Hence not preferred.

Treatment of Asthma

Mild asthma—Rapidly acting, inhaled β_2 stimulants like salbutamol.

Moderate asthma—Regular prophylaxis with cromoglycate. If the patient does not respond to cromolyn—inhaled steroids are given for prophylaxis. Acute episodes are managed with inhaled β_2 agonists.

Severe asthma

- a. Regular inhaled steroids
- b. Inhaled β_2 agonists 3-4 times a day

- c. Oral steroids may be considered
- d. Additional inhaled ipratropium bromide or oral theophylline may be given.

Acute severe asthma or status asthmaticus is an acute exacerbation. It is a medical emergency; may be triggered by an acute respiratory infection, abrupt withdrawal of steroids after prolonged use, by drugs, allergens or emotional stress.

Treatment

1. Nebulization of β_2 agonist and ipratropium alternately—every 30 minutes. Additional salbutamol 0.4 mg IM/SC may be given. Severe tachycardia should be watched for.
2. Hydrocortisone hemisuccinate IV 100 mg stat followed by 100 mg every 8 hours infusion followed by a course of oral prednisolone.
3. Oxygen inhalation.
4. Antibiotics - if infection is present.
5. IV fluids to correct dehydration and acidosis.
6. Aminophylline 250 mg slow IV over 15-20 minutes has been used by some physicians should be given carefully—watching for adverse effects but is now not preferred.
7. Artificial ventilation may be required in extreme cases.

Bronchial Asthma and Dentistry

1. A small amount of water or dental materials used in dental procedures may aspirate into the respiratory passage and trigger an acute attack of bronchial asthma. Salbutamol inhalation should be given immediately. The dental procedure may be continued after the patient recovers.
2. Analgesics (NSAIDs) prescribed for relief of pain may trigger acute episodes of

asthma. This should be kept in mind. Depending on the severity of asthma and the dose of the NSAID required, appropriate drug should be prescribed. If the patient has severe asthma and requires an antiinflammatory drug for his dental problem prednisolone should be considered.

3. If the patient has been receiving steroid inhalation for prophylaxis of bronchial asthma for a long period, the oral microflora could be altered. This predisposes the oral mucosa to infection with microorganisms like candida and certain bacteria. Appropriate care should be taken.

DRUGS USED IN THE TREATMENT OF COUGH

Cough is a protective reflex that removes the irritant matter and secretions from the respiratory tract. It could be due to infection, allergy, pleural diseases and malignancy. Since it is a protective mechanism, undue suppression of cough can cause more harm than benefit. In some conditions, as in dry annoying cough, it may serve no useful purpose. In such situations, antitussives or cough suppressants may be used. Antitussives only provide symptomatic relief and do not alter the cause.

Antitussives

1. Central cough suppressants
Codeine, pholcodeine, noscapine, dextromethorphan, antihistamines, benzonatate.
2. Pharyngeal demulcents
Lozenges, cough drops, linctuses
3. Expectorants
Potassium iodide, Guaiphenesin, ammonium chloride, ipecacuanha

Central Cough Suppressants

Central cough suppressants act by inhibiting cough centre in the medulla.

Codeine is a good antitussive with less addiction liability. However, nausea, constipation and drowsiness are common. *Dose* 10-15 mg every 6 hours (See page 164). *Noscapine* is a natural opium alkaloid which is a potent antitussive. No other CNS effects are prominent in therapeutic doses (See page 164). Nausea is the only occasional side effect. *Dose* 15-30 mg every 6 hours.

Dextromethorphan and *pholcodeine* are synthetic opioid derivatives with antitussive actions like codeine but with lesser side effects. Pholcodeine is longer-acting - given twice daily.

Benzonatate is chemically related to the local anaesthetic procaine. It acts on the cough receptors in the lungs and also has a central effect. It is given orally - 100 mg thrice daily.

Antihistamines are useful in cough due to allergy except that due to bronchial asthma. They thicken the secretions which may be difficult to cough out. An antihistamine is generally one of the components of cough syrups. Their sedative property may be of additional value in suppressing cough.

Other centrally acting antitussives include carbetapentane, chlrophedianol and caramiphen. More extensive studies are required to prove their efficacy.

Pharyngeal Demulcents

Pharyngeal demulcents (**demulcere** = to caress soothingly - in LATIN) increase the flow of saliva which produces a soothing effect on the pharyngeal mucosa and reduce afferent impulses arising from the irritated mucosa. Dry cough due to irritation of the pharyngeal mucosa is relieved. Candy sugar or a few drops of lemon also serve this purpose.

Expectorants

Expectorants (Latin - *expectorare* = to drive from the chest) increase the production of respiratory tract secretions which cover the irritated mucosa. As the secretions become thin and less viscid, they can be easily coughed out. Expectorants may increase the secretions directly or reflexly.

- *Direct stimulants* Volatile oils like eucalyptus oil; creosotes, alcohol, cedar wood oil - when administered by inhalation with steam can increase respiratory secretions.
- *Reflex expectorants* are given orally, they are gastric irritants and reflexly increase respiratory secretions.

Potassium iodide acts both directly and reflexly.

Ipecacuanha is an emetic. In sub-emetic doses it is used as an expectorant.

Bronchodilators

Bronchodilators like salbutamol and terbutaline relieve cough that results from bronchospasm.

The antitussive preparations generally have a combination of a central cough suppressant, an expectorant, an antihistaminic and sometimes a bronchodilator and a mucolytic agent.

Mucolytics

Normally the respiratory mucous is watery. The glycoproteins in the mucous are linked by disulphide bonds to form polymers making it slimy. In respiratory diseases, the glycoproteins form larger polymers with

plasma proteins present in the exudate and the secretions become thick and viscid. Mucolytics liquefy the sputum making it less viscid so that it can be easily expectorated.

The following are mucolytics -

Bromhexine, a semisynthetic compound related to vasicine (an alkaloid from the plant *Adhatoda vasica*) is a good mucolytic. It depolymerises the mucopolysaccharides in the mucus. It is given orally (8-16 mg thrice daily). Side effects are minor - may cause rhinorrhoea.

Ambroxol is a metabolite of bromhexine with actions similar to it. Ambroxol may be given orally or by inhalation. It can be used as an alternative to bromhexine.

Acetylcysteine opens disulfide bonds in mucoproteins of the sputum reducing its viscosity. It is given by aerosol. Side effects are common and hence not preferred.

Carbocysteine Carbocysteine is similar to acetylcysteine and is used orally.

Pancreatic dornase Deoxyribonuclease is a major component of the purulent respiratory tract secretions. Pancreatic dornase is a deoxyribonuclease obtained from the beef pancreas. It breaks the deoxyribonucleic acid (DNA) into smaller parts thus making the secretions thin and less viscid. It is administered by inhalation.

Pancreatic dornase can cause allergic reactions.

Steam inhalation offers an effective and inexpensive alternative to drugs. It humidifies the sputum as well as respiratory mucosa. This helps in reducing the irritation and for easier expectoration of the sputum. In presence of dehydration, just rehydrating the patient is found to be beneficial.

Haematopoietic System

HAEMATINICS

Haematinics are compounds required in the formation of blood and are employed in the treatment of anaemias. Haematinics include iron, vitamin B₁₂ and folic acid. Haematopoietic growth factors are also discussed here.

Iron

Iron, vitamin B₁₂ and folic acid are essential for normal erythropoiesis.

Iron is essential for haemoglobin production. Total body iron is about 2.5 to 5 grams, two-thirds of which is present in haemoglobin. Each molecule of haemoglobin has 4 iron containing residues. It is also present in myoglobin, the cytochromes and other enzymes.

Distribution of Iron in the Body

Haemoglobin	66%
Ferritin, haemosiderin	25%
Myoglobin (in muscles)	03%
Enzymes (cytochromes, etc.)	06%

Daily Requirement of Iron

Adult male	0.5-1 mg
Adult female	1-2 mg
Pregnancy and lactation	3-5 mg

Dietary sources of iron Food items that are rich in iron are liver, egg yolk, meat, fish, chicken, spinach, dry fruits, wheat and apple.

Absorption

The average Indian diet provides about 10-20 mg of iron. 10 percent of this iron is absorbed. Dietary iron may be present as haeme or as inorganic iron. It is mostly absorbed from the upper gut in the ferrous form. During deficiency, absorption is better. Haeme iron is better absorbed than inorganic iron.

Factors that Influence Iron Absorption

Ascorbic acid, amino acids, meat, ↑gastric acidity – Increase absorption.

Antacids, phosphates, phytates, tetracyclines presence of food in the stomach—Decrease absorption.

Transport and Distribution

Iron is transported with the help of a glycoprotein *transferrin* and stored as *ferritin* and *haemosiderin*, in liver, spleen and bone marrow.

Excretion

Daily 0.5-1 mg of iron is excreted. A large part is lost in shedding of intestinal mucosal cells and small amounts in the bile, desquamated skin and urine. In females, iron is also lost in menstruation.

Preparations of Iron

Iron is generally given orally—but can be given parenterally.

Oral Iron Preparations

1. Ferrous sulphate–200 mg tab
2. Ferrous fumarate–200 mg tab
3. Ferrous gluconate–300 mg tab
4. Ferrous succinate–100 mg
5. Iron calcium complex–5% iron
6. Ferric ammonium citrate–45 mg.
 - Ferrous salts are better absorbed than ferric salts and are cheaper.
 - The last three preparations given above are claimed to be better tolerated but are more expensive.
 - Expensive preparations of iron with vitamins, liver extract, amino acids, etc. are available but offer no obvious benefits.
 - *Dose* Ferrous sulphate 200 mg - 3-4 tablets daily. The elemental iron content of different salts varies.

Adverse Effects of Oral Iron

Epigastric pain, nausea, vomiting, gastritis, metallic taste, constipation (due to astringent effect) or diarrhoea (irritant effect) are the usual adverse effects. Liquid preparations of iron cause staining of the teeth.

Parenteral Iron

Intramuscular injection of iron is given deep IM in the gluteal region using 'Z' technique to avoid staining of the skin. Intravenous iron is given slowly over 5-10 minutes or as infusion after a test dose.

Indications

1. When oral iron is not tolerated
2. Failure of absorption—as in malabsorption, chronic bowel disease
3. Noncompliance
4. Severe deficiency with bleeding.

Preparations

1. Iron dextran has 50 mg elemental iron/ml (2 ml ampoule) - it is the only preparation that can be given intravenously. It can also be given IM.
2. Iron-sorbitol-citric acid complex—contains 50 mg elemental iron/ml; given *only IM*. This preparation should not be given IV because it quickly saturates the transferrin stores. As a result free iron levels in the plasma rises and can cause toxicity. Dose is to be calculated using a formula.

$$\text{Iron requirement} = \frac{4.4 \times \text{body weight} \times \text{Hb deficit}}{(\text{mg}) \quad (\text{kg}) \quad (\text{g/dl})}$$
 This also includes iron needed for replenishment of stores.

Adverse Effects

Local Pain at the site of injection, pigmentation of the skin and sterile abscess.

Systemic Fever, headache, joints pain, palpitation, difficulty in breathing, lymph node enlargement and rarely anaphylaxis.

Acute iron poisoning is common in infants and children in whom about 10 tablets (1-2 g) can be lethal. Manifestations include vomiting, abdominal pain, haematemesis, bloody diarrhoea, shock, drowsiness, cyanosis, acidosis, dehydration, cardiovascular collapse and coma. Immediate diagnosis and treatment are important as death may occur in 6-12 hr.

Treatment

- Gastric lavage with sodium bicarbonate solution.
- Desferrioxamine is the antidote. It is instilled into the stomach after lavage, to prevent iron absorption; injected IV/IM.
- Correction of acidosis and shock.

Table 33.1: Daily requirement of vitamin B₁₂ and folic acid

	Adults	Pregnancy and lactation
Vitamin B ₁₂	1-3 µg	3-5 µg
Folic acid	50-100 µg	200-400 µg

As 50% of ingested drug is lost, double the amount is recommended for daily dietary intake

Indications for Iron

Iron deficiency anaemia—both for the prophylaxis and treatment. The cause for iron deficiency should be identified. Treatment should be continued depending on the response for 3-6 months to replenish iron stores. Prophylactically iron is given in conditions with increased iron requirement as in pregnancy, infancy and professional blood donors.

VITAMIN B₁₂ AND FOLIC ACID

Vitamin B₁₂ and folic acid are water soluble vitamins, belonging to the B-complex group. They are essential for normal DNA synthesis. Their deficiency leads to impaired DNA synthesis and abnormal maturation of RBCs and other rapidly dividing cells. This results in megaloblastic anaemia, characterised by the presence of red cell precursors in the blood and bone marrow. Vitamin B₁₂ and folic acid are therefore called maturation factors. Other manifestations of deficiency include glossitis, stomatitis and malabsorption; neurological manifestations can also result.

Vitamin B₁₂

Vitamin B₁₂ (Cyanocobalamin) is synthesized by microorganisms. Liver, fish, egg yolk, meat, cheese and pulses are the dietary sources of B₁₂.

Vitamin B₁₂ or extrinsic factor is absorbed with the help of intrinsic factor, a protein

secreted by the stomach. It is carried in the plasma by B₁₂-binding proteins called *transcobalamin* and is stored in the liver.

Functions

Vitamin B₁₂ and folic acid act as coenzymes for several vital metabolic reactions and are essential for DNA synthesis.

Daily requirement— (Table 33.1).

Deficiency

B₁₂ deficiency may be due to:

1. *Addisonian pernicious anaemia* Thomas Addison first described cases of anaemia not responding to iron. There is deficiency of intrinsic factor due to destruction of parietal cells resulting in failure of B₁₂ absorption.
2. *Other causes* Gastrectomy, chronic gastritis, malabsorption and fish tapeworm infestation (fish tapeworm consumes B₁₂).

Preparations

- Cyanocobalamin—100 µg/ml injection may be given IM or deep SC - hypersensitivity reactions can occur.
- Hydroxocobalamin—100, 500, 1000 µg/ml injection-has longer lasting effect but hydroxocobalamin administration can result in the formation of antibodies.
- Multivitamin preparations contain variable amounts of vitamin B₁₂ with or without intrinsic factor for oral use.

Uses

1. *B₁₂ deficiency* Prophylaxis and treatment of megaloblastic anaemia due to B₁₂ deficiency of any cause. If B₁₂ deficiency is due to lack of intrinsic factor, it is given IM or SC. Pernicious anaemia needs life long treatment with B₁₂. Oral folic acid should be added because B₁₂ induced brisk haemopoiesis may also increase the demand for folic acid. Prophylactic dose of vitamin B₁₂ is 3-10 µg daily.
2. *B₁₂ neuropathies* like subacute combined degeneration respond to vitamin B₁₂.

Folic Acid

Folic acid is pteroylglutamic acid. It was first isolated from spinach and therefore named as folic acid (from leaf).

Dietary source Green vegetables, liver, yeast, egg, milk and some fruits. Prolonged cooking with spices destroys folic acid.

Absorption takes place in the duodenum and jejunum and is transported in the blood by active and passive transport, widely distributed in the body and is stored in the liver.

Functions Folic acid is converted to dihydrofolic acid and then to tetrahydrofolic acid which serves as a coenzyme for many vital (one-carbon transfer) reactions necessary for DNA synthesis.

Deficiency Folate deficiency may be due to dietary folate deficiency, malabsorption and other diseases of the small intestine or drug induced. Phenytoin, phenobarbitone, oral contraceptives, methotrexate and trimethoprim can induce folate deficiency. Increased requirement as in growing children, pregnancy and lactation can also cause deficiency. Manifestations include megaloblastic anaemia, glossitis, diarrhoea and weakness.

Uses

1. Megaloblastic anaemia due to folate as well as B₁₂ deficiency—folic acid 2-5 mg/day is given orally along with vitamin B₁₂. In folic acid deficiency due to malabsorption syndromes, folic acid is given IM.
2. Prophylactically in pregnancy, lactation, infancy and other situations with increased requirement of folic acid - 500 µg daily orally.

Folinic acid (citrovorum factor, leucovorin) is N-formyl tetrahydrofolic acid and is the active coenzyme form which overcomes methotrexate toxicity (Page 330).

HAEMATPOIETIC GROWTH FACTORS

Haematopoietic growth factors are hormones that regulate erythropoiesis. Many of these glycoproteins have now been produced for clinical use by recombinant DNA technology. Frequent blood counts are needed to monitor therapy with these growth factors.

Haematopoietic Growth Factors Include:

- Erythropoietin
- Myeloid growth factors
 - GM-CSF
 - G-CSF
 - M-CSF
- Megakaryocyte growth factors
 - Thrombopoietin
 - Interleukin-II

Erythropoietin is produced by the kidney in response to hypoxia and anaemia. It binds to erythropoietin receptors on red cell progenitors and stimulates red cell production.

It can cause hypertension, thrombosis and allergic reactions. Parenteral iron may be needed to prevent iron deficiency that is precipitated by rapid erythropoiesis.

Uses - Erythropoietin is useful in the treatment of anaemia seen in chronic renal failure, bone marrow disorders, malignancies, chronic

inflammation and anaemia associated with AIDS.

Myeloid growth factors include granulocyte - macrophage colony stimulating factor (GM-CSF), Granulocyte colony stimulating factor (G-CSF) and Monocyte colony stimulating factor (M-CSF). Recombinant human GM-CSF is sargramostim and G-CSF is filgrastim. They bind to specific receptors on the myeloid progenitor cells and stimulate the proliferation and differentiation of neutrophils and monocytes.

Adverse effects include bone pain, fever, arthralgia, myalgia and dyspnoea.

Myeloid growth factors are used in bone marrow transplantation, following cancer chemotherapy, aplastic anaemia, congenital neutropenia, myelodysplasia and in AIDS patients with neutropenia.

Megakaryocyte Growth Factors

Thrombopoietin increases the production of platelets. It is being tried in severe thrombocytopaenia as that seen following cancer chemotherapy.

DRUGS USED IN THE DISORDERS OF COAGULATION

Haemostasis is the spontaneous arrest of bleeding from the damaged blood vessels. In the process, complex interactions take place between the injured vessel wall, platelets and clotting factors.

Following injury, there is local vasoconstriction and platelet adhesion—forming a plug which temporarily stops bleeding. This is reinforced by fibrin for long-term haemostasis.

Clotting factors are proteins synthesized by the liver. Two systems—the extrinsic and the intrinsic system are involved in the process of coagulation. Several proteins interact in a cascading series to form the clot (Fig. 33.1).

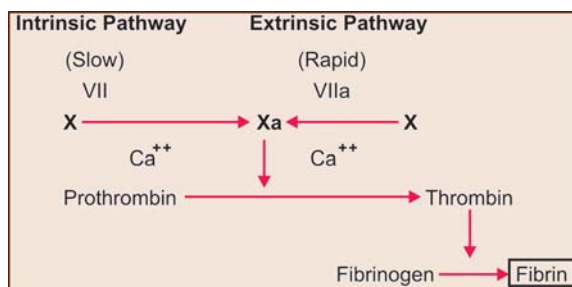


Fig. 33.1: Major reactions of blood coagulation

Anticoagulants are drugs that reduce the coagulability of the blood.

Classification

1. *Anticoagulants used in vivo*
 - A. *Fast acting*
 - Heparin
 - Low mol. wt. heparins
 - Heparinoids -
 - Heparan sulphate
 - Dextran sulphate
 - Danaparoid
 - Lepirudin
 - B. *Slow acting*
(oral anticoagulants)
 - *Coumarin derivatives:*
 - Bishydroxycoumarin
 - Warfarin sodium
 - Nicoumalone
 - *Indandione derivatives:*
 - Phenindione
 - Diphenadione
2. *Anticoagulants used in vitro*
 - Heparin
 - Citrates, Oxalates
 - Sodium edetate.

HEPARIN AND HEPARINOID

Heparin was discovered by McLean, a medical student in 1916. It was named 'heparin' as it was first extracted from the liver. It is a

mucopolysaccharide found in the mast cells of the liver, lungs and intestinal mucosa. Heparin is the strongest acid in the body. It is a glycosaminoglycan.

Actions Heparin is a powerful anticoagulant that acts instantaneously both *in vivo* and *in vitro*.

Mechanism of Action: Antithrombin III is a peptide that is synthesized in the liver and circulates in the plasma. Heparin activates plasma antithrombin III (Fig. 33.3). Antithrombin III binds to and inhibits the activated thrombin and coagulation factors (Xa and IXa). This is a physiological reaction, but heparin accelerates it by 1000 times. Clotting time is prolonged. The heparin-antithrombin III complex inhibits activated factor X and thrombin, while low molecular weight (LMW) heparin only inhibits factor X and not thrombin (Table 33.2).

Other actions Heparin activates lipoprotein lipase which hydrolyses triglycerides present in the plasma and thus clears the plasma of lipids.

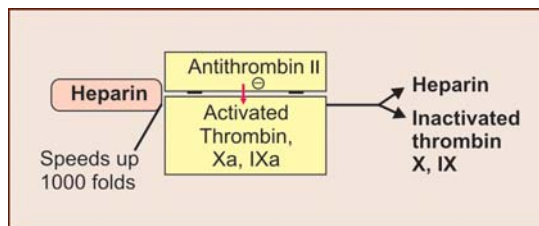


Fig. 33.3: Mechanism of action of heparin

Pharmacokinetics Heparin is not effective orally. It is given IV or SC. It should not be given IM because it may cause haematomas, due to local bleeding, absorption is erratic and also causes irritation. Given intravenously the onset of action is immediate, reaches peak in 5-10 minutes and clotting time returns to normal in 2-4 hours. Treatment is monitored by aPTT (preferable) or clotting time. Heparin is metabolised by heparinase in the liver.

Heparin is given as a bolus dose of 5000 units followed by a maintenance dose of 1000 units/hour as infusion.

Adverse Reactions

1. **Bleeding** is the most common, major adverse effect of heparin. Careful monitoring and

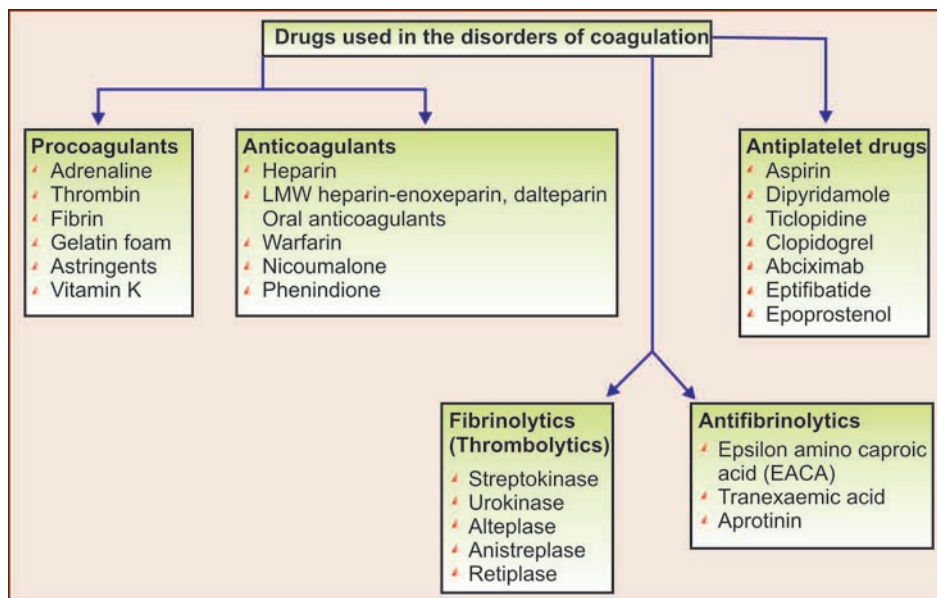


Fig. 33.2: Drugs used in the disorders of coagulation

Table 33.2: Compare and contrast standard heparin and LMW heparin

Features	Standard Heparin	LMW Heparin
Mol. Weight	10,000-20,000	4,000-7,000
Source	Natural	Semisynthetic (Chemical treatment of std. heparin)
Thrombin activity in therapeutic doses	Inhibited	Not inhibited
Effect on tests of clotting	Significant	Not significant
Lab. monitoring	Required	Not required
SC Bioavailability	Short (20-30%)	(70-90%)
Duration of action	Short (2-4 hrs)	Long (18-24 hrs)
Frequency of administration	Every 4-6 hrs	Once a day
Thrombocytopenia	Can occur	Lesser Chances
Risk of bleeding	Present	Lower

dose control will prevent this to a great extent.

2. *Hypersensitivity reactions* For commercial use heparin is obtained from bovine lung or porcine intestine. Because of its animal origin allergic reactions are quite common.
3. *Thrombocytopenia* Heparin induced platelet aggregation and formation of antiplatelet antibodies both result in thrombocytopenia. The antigen antibody complexes may damage the vessel wall triggering thrombosis and disseminated intravascular coagulation. This paradoxical complication of heparin therapy is rare but can be serious. Heparin should be stopped immediately at the first sign of thrombocytopenia.
4. *Alopecia* is reversible.
5. *Osteoporosis* - on long-term use - the cause is unknown.
6. *Hypoaldosteronism* - Heparin can inhibit the synthesis of aldosterone and may result in hyperkalemia.

Contraindications to heparin therapy

Bleeding disorders, thrombocytopenia, haemophilia, severe hypertension, intracranial haemorrhage, cirrhosis, ulcers in the gut, renal failure and neurosurgery.

Low molecular weight (LMW) heparins, e.g. enoxaparin, dalteparin, tinzaparin, ardeparin and reviparin have a mol. wt. of 4000-7000. LMW heparins are obtained by chemical/enzymatic treatment of standard heparin. LMW heparins inhibit factor Xa like conventional heparin but differ from it as follows - in therapeutic doses LMW heparins do not inhibit thrombin activity (because they are too short). In therapeutic doses, LMW heparins do not have significant effect on the tests of clotting. Therefore lab monitoring is not required. Apart from being equally efficacious, LMW heparins have a favourable pharmacokinetic profile and have the following advantages over standard heparins-

- Better bioavailability following SC injection.
- Longer action
- Lower risk of bleeding (because of less interaction with platelets)
- Lower risk of osteoporosis
- Lower incidence of thrombocytopenia (because less antigenic) and thrombosis
- Routine lab monitoring not required.

Uses - LMW heparins are used in-

- The prevention and treatment of venous thrombosis and pulmonary embolism

- In unstable angina
- To maintain the patency of tubes in dialysis patients.

Heparin antagonist Mild heparin overdosage can be treated by just stopping heparin because heparin is short acting. In severe heparin overdose, an antagonist may be needed to arrest its anticoagulant effects. *Protamine sulphate* is a protein obtained from the sperm of certain fish. Given intravenously, it neutralises heparin (1 mg for every 100 units of heparin). In the absence of heparin, protamine sulphate can itself act as a weak anticoagulant. Hence overdose should be avoided. Protamine sulphate is a strongly basic protein which binds with the strongly acidic groups of heparin forming a stable complex which is devoid of anticoagulant activity—this is the pharmacological basis for using protamine sulphate in heparin overdosage.

Whole blood transfusion may be needed.

Heparinoids

Heparan sulfate present in some tissues is similar to heparin. It is believed to be responsible for antithrombotic activity on the vascular endothelium.

Hirudin is the anticoagulant found in the salivary glands of leeches. It is a powerful thrombin inhibitor. *Lepirudin* is produced by recombinant DNA technology and can be used in patients allergic to heparin but it has no antagonist yet.

Danaparoid is a mixture of heparinoids and acts by inhibiting factor Xa. It does not prolong aPTT and is longer acting. It is used subcutaneously in the treatment of deep vein thrombosis and in other conditions as an alternative to heparin.

ORAL ANTICOAGULANTS

Cattle that were fed on spoiled sweet clover hay, developed a haemorrhagic disease in

North America in 1924. This turned out to be due to bishydroxycoumarin, an anticoagulant in the spoiled sweet clover. Many related compounds were then developed and are also being used as rat poison.

Mechanism of action Warfarin and its congeners act as anticoagulants only *in vivo* because they act by interfering with the synthesis of vitamin K dependent clotting factors in the liver. They block the γ carboxylation of glutamate residues in prothrombin, factors VII, IX and X. γ carboxylation is necessary for these factors to participate in coagulation.

The onset of action is slow; anticoagulant effect develops over 1-3 days because oral anticoagulants do not destroy the already circulating clotting factors. Prothrombin time (PT) is measured to monitor the treatment. It takes 5-7 days for PT to return to normal after stopping oral anticoagulants.

Pharmacokinetics Warfarin is completely absorbed orally and is 99% bound to plasma proteins.

Adverse Effects

1. Haemorrhage is the main hazard. Bleeding in the intestines or brain can be troublesome. Minor episodes of epistaxis and bleeding gums are common.

Treatment—depends on the severity:

- a. Stop the anticoagulant.
 - b. Fresh blood transfusion is given to supply clotting factors.
 - c. *Antidote* The specific antidote is *vitamin K₁ oxide*. It allows synthesis of clotting factors. But even on IV administration, the response to vitamin K₁ oxide needs several hours. Hence in emergency, *fresh whole blood* is necessary to counter the effects of oral anticoagulants.
2. Other adverse effects include allergic reactions, gastrointestinal disturbances and teratogenicity.

Factors influencing oral anticoagulant activity

<i>Factors enhancing activity</i>	<i>Factors reducing activity</i>
Poor diet, bowel disease, liver disease and chronic alcoholism—result in vitamin K deficiency	Pregnancy—there is increased synthesis of clotting factors Hypothyroidism—there is reduced degradation of clotting factors.

*Drug Interactions**Many drugs potentiate warfarin action*

1. Drugs that inhibit platelet function—NSAIDs like aspirin increase the risk of bleeding.
2. Drugs that inhibit hepatic drug metabolism like cimetidine, chloramphenicol and metronidazole enhance plasma levels of warfarin.

Some drugs *reduce* the effect of oral anticoagulants.

1. Drugs that enhance the metabolism of oral anticoagulants—microsomal enzyme inducers like barbiturates, rifampicin, griseofulvin enhance the metabolism of oral anticoagulants. When these drugs are suddenly withdrawn, excess anticoagulant activity may result in haemorrhages.
2. Drugs that increase the synthesis of clotting factors – oral contraceptives.

Uses of Anticoagulants

Anticoagulants can prevent the extension of thrombus but cannot destroy the existing clots. Heparin has rapid and short action which makes it suitable for initiating treatment (Table 33.3) while warfarin is suitable for long-term maintenance due to its slow and prolonged action and convenience of oral use.

1. *Venous thrombosis and pulmonary embolism*—anticoagulants prevent extension of thrombus and recurrence of embolism.
2. *Postoperative, post-stroke patients; bedridden patients* due to leg fractures and other causes—who cannot be ambulant for several months – anticoagulants prevent venous thrombosis and pulmonary embolism in such patients.
3. *Rheumatic valvular disease*—anticoagulants prevent embolism.

Table 33.3: Differentiating features between Heparin and Dicoumarol/Warfarin

<i>Features</i>	<i>Heparin</i>	<i>Dicoumarol/warfarin</i>
1. Source	Natural	Synthetic
2. Chemistry	Mucopolysaccharide	Coumarin derivative
3. Site of action	Parenteral	Oral
4. Route of administration	<i>In vivo</i> and <i>In vitro</i>	<i>In vivo</i> only
5. Onset of action	Immediate	Slow (1-3 days)
6. Duration of action	Short (2-4 hours)	Long (4 -7 days)
7. Mechanism	Activates antithrombin III which inhibits thrombin and Xa and IX a	Inhibits synthesis of clotting factors (II, VII, IX, X)
8. Antagonist	Protamine sulfate	Vit. K ₁ oxide
9. Monitoring with	aPTT/clotting time	Prothrombin time
10. Used for	Initiation of therapy	Maintenance therapy

4. *Unstable angina*—heparin reduces the risk of myocardial infarction in patients with unstable angina.
5. *Vascular surgery, artificial heart valves and haemodialysis*—anticoagulants prevent thromboembolism.

Contraindications to anticoagulant therapy

- Bleeding disorders including thrombocytopenia
- Severe hypertension
- Malignancies
- Bacterial endocarditis
- Liver and kidney diseases.
- Recent surgery (in the last 10-15 days)
- History of cerebrovascular accident

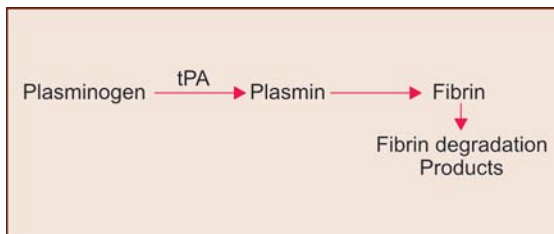
THROMBOLYTICS (FIBRINOLYTICS)

Thrombolytics lyse the clot or thrombi by activating the natural fibrinolytic system.

Plasminogen circulates in the plasma and also some of it is bound to fibrin. Tissue plasminogen activator (tPA) activates plasminogen which is converted to plasmin. Plasmin degrades fibrin thereby dissolving the clot. Thrombolytic agents are *streptokinase*, *urokinase*, *alteplase* and *reteplase*. All are expensive drugs.

Streptokinase obtained from β -haemolytic streptococci activates plasminogen. Anti-streptococcal antibodies present in the blood due to previous streptococcal infections inactivate a large amount of streptokinase.

Streptokinase is antigenic and can cause allergy. The antibodies formed may persist for five years. Hence if thrombolytics are required during that period, others like tPA or urokinase should be used. Streptokinase also causes hypotension.



Anistreplase

Anistreplase (Anisoylated plasminogen streptokinase activator complex) is a form of streptokinase which is long acting and can be injected in a single IV bolus. Hence it is more convenient to use.

Urokinase

Urokinase is an enzyme prepared from cultures of human kidney cells (it was first isolated from human urine—hence the name). It activates plasminogen. It is more expensive than streptokinase.

Tissue Plasminogen Activator

Tissue plasminogen activator (tPA) preferentially activates plasminogen that is bound to fibrin (clot) which means circulating plasminogen is largely spared.

Alteplase, Duteplase

Alteplase, duteplase are tPA produced by recombinant DNA technology. They are very expensive.

Reteplase

Reteplase is modified human tPA obtained by genetic engineering. It is claimed to have the following advantages over tPA

- faster reperfusion
- bleeding tendency is negligible.

Tenecteplase

Tenecteplase is longer acting and can be given as an IV bolus injection. Its ability to bind fibrin is better than that of alteplase.

Adverse Effects of Thrombolytics

Bleeding is the major toxicity of all thrombolytics. Hypotension and fever can occur. Allergic reactions are common with streptokinase.

Uses

1. Acute myocardial infarction—Intravenous thrombolytics given immediately reduce the mortality rate in acute MI. They should be given within 12 hours but preferably immediately because early treatment largely reduces mortality.
2. Deep vein thrombosis and large pulmonary emboli are also treated with fibrinolytics.

Contraindications to thrombolytic therapy

- Recent surgery, injury, gastrointestinal bleeding, stroke.
- Severe hypertension.
- Bleeding disorders.

ANTIFIBRINOLYTICS

Antifibrinolytics inhibit plasminogen activation and thus prevent fibrinolysis.

Epsilon aminocaproic acid (EACA) and its analogue *tranexamic acid* are antifibrinolytics. They bind to plasminogen and plasmin and prevent the binding of fibrin to these proteins. *Aprotinin* is another fibrinolytic drug which acts by inhibiting proteolytic enzymes. Antifibrinolytics are used in overdose of fibrinolytics and to reduce bleeding after prostatic surgery and some patients undergoing cardiac surgeries or after tooth extraction in haemophiliacs—but the beneficial effect is uncertain.

ANTIPLATELET DRUGS

Platelets form the initial haemostatic plug at the site of vascular injury and are also involved in the formation of atherosclerosis. By inhibiting the platelet function, thrombosis and atherosclerotic vascular disease can be largely prevented.

Antiplatelet drugs or drugs interfering with platelet function include -

1. *PG synthesis inhibitors* - Aspirin
2. *Phosphodiesterase inhibitor* - Dipyridamol
3. *ADP antagonists* - Ticlopidine
Clopidogrel
4. *Glycoprotein IIb/IIIa receptor antagonists* - Abciximab
Eptifibatide
Tirofiban
5. *Others*- PGI₂
Aspirin (see chap 27) Thromboxane A₂ promotes platelet aggregation. Aspirin inactivates cyclo-oxygenase (COX) and thereby inhibits the synthesis of thromboxane A₂ even in low doses (75 mg/day). The COX inhibition is irreversible and the effect lasts for 7 to 10 days—till fresh platelets are formed. Aspirin is the most commonly used antiplatelet drug.
Dipyridamole is a phosphodiesterase inhibitor which interferes with platelet function by increasing platelet cyclic AMP levels. It is used along with aspirin for the prophylaxis of thromboemboli in patients with prosthetic heart valves.

ADP Antagonists

Ticlopidine ADP binds to receptors on platelets to bring about platelet aggregation. Ticlopidine is a prodrug. Its active metabolite blocks ADP receptors and prevents platelet aggregation. Onset of action is slow (7-11 days) and the antiplatelet effect remains for some days even after stopping the drug. Dose: 250 mg twice daily. Adverse effects include dyspepsia, diarrhoea, bleeding and leukopenia. It is used in patients who cannot tolerate aspirin.

Clopidogrel has structural similarity to ticlopidine with similar mechanism of action. Like ticlopidine it is a prodrug and the active

metabolite blocks ADP receptors. Its actions are additive with aspirin as the mechanisms are different. Toxicity is milder with lesser incidence of leukopenia and thrombocytopenia.

Clopidogrel is used as an alternative when aspirin cannot be used. It can also be used with aspirin for additive effects.

Glycoprotein IIb/IIIa receptor antagonists
Fibrinogen and von Willebrand factor bind to glycoprotein IIb/IIIa receptors on the platelets and mediate platelet aggregation by platelet agonists like thrombin, collagen and TXA_2 . Drugs that block these receptors inhibit platelet aggregation induced by all platelet agonists.

Abciximab is a monoclonal antibody which binds GP IIb/IIIa receptors and inhibits platelet aggregation. It can cause bleeding and allergic reactions. It is used in patients undergoing coronary angioplasty.

Eptifibatide and tirofiban are peptides given as IV infusion. They are short acting and are tried in unstable angina and myocardial infarction.

Others

Epoprostenol (PGI_2) can be used during haemodialysis to prevent platelet aggregation as an alternative to heparin.

Uses of Antiplatelet Drugs

1. *Myocardial infarction* Aspirin with thrombolytics improves survival in acute MI. Long-term treatment with aspirin reduces reinfarction in post MI patients.
2. *Unstable angina and stable angina pectoris* Aspirin reduces the risk of acute MI. Clopidogrel may be added to aspirin in unstable angina.
3. In patients with prosthetic heart valves, valvular heart disease, coronary artery by-

pass surgery—long-term use of low dose aspirin is recommended.

4. *Cerebral thrombosis and TIA* In patients with transient ischaemic attacks aspirin reduces the incidence of stroke and mortality. In cerebral thrombosis aspirin prevents recurrence.
5. *Atrial fibrillation* If oral anticoagulants can not be given, aspirin is useful.

COAGULANTS

Coagulants are drugs that promote coagulation (procoagulants) and control bleeding. They are also called *haemostatics*. They may be used locally or systemically. Local haemostatics are called *styptics*. Physical methods like local application of pressure, tourniquet or ice can control bleeding.

Styptics are local haemostatics that are used on bleeding sites like tooth socket and wounds.

They are:

1. *Adrenaline* Sterile cotton soaked in 1:10,000 solution of adrenaline is commonly used in tooth sockets and as nasal packs for epistaxis. Adrenaline arrests bleeding by vasoconstriction.
2. *Thrombin* powder is dusted over the bleeding surface following skin grafting. It is obtained from bovine plasma.
3. *Fibrin* obtained from human plasma is available as sheets. It is used for covering or packing bleeding surfaces.
4. *Gelatin foam* is porous spongy gelatin used with thrombin to control bleeding from wounds. It gets completely absorbed in 4 to 6 weeks and can be left in place after suturing of the wound.
5. *Thromboplastin powder* is used in surgery as a styptic.
6. *Astringents* like tannic acid are used on bleeding gums.

Coagulants Used Systemically are

- Vitamin K
- Fibrinogen
- Specific deficient factor—factors, II, VII, VIII, IX, X
- Ethamsylate

Vitamin K

Vitamin K is a fat-soluble vitamin essential for the biosynthesis of clotting factors. There are three compounds:

- Vitamin K₁— present in food from plant source
- Vitamin K₂— produced in the gut by bacteria.
- Vitamin K₃— a synthetic compound used therapeutically.

Actions Vitamin K is essential for the biosynthesis of clotting factors—prothrombin and factors VII, IX and X by the liver.

Human requirement—Not clearly known—recommended intake in adults is 50-70 mg/day

Deficiency—Vitamin K deficiency results from liver diseases, malabsorption, long-term antibiotic therapy and rarely by dietary deficiency. It is manifested as bleeding tendencies.

Adverse reactions are seen on parenteral administration of vitamin K—allergic reactions and jaundice can occur.

Uses

1. Vitamin K deficiency
2. *Newborn babies* lack intestinal flora and have low levels of prothrombin and other clotting factors. Routine administration of vitamin K—1 mg IM prevents haemorrhagic disease of the newborn.
3. Oral anticoagulant toxicity.

OTHER COAGULANTS

- Fresh plasma or whole blood is useful in most coagulation disorders as it contains all the clotting factors.
- Concentrated plasma fractions like fibrinogen, factors VIII, II, VII, IX and X are available for the treatment of specific deficiencies.
- *Snake venom* Some venoms like Russels viper venom stimulate thrombokinase and promote coagulation.
- Ethamsylate is used orally to arrest bleeding. The exact mode of action is not known but it is thought that it acts by inhibiting the synthesis of prostacycline (PGI₂) and correct the abnormal platelet function. It may also stabilize the wall of the capillaries and reduce capillary bleeding. Ethamsylate is given orally to control bleeding in—
 1. Dental extraction and other procedures in patients with coagulation disorders.
 2. Menorrhagia
 3. Post-partum haemorrhage.
 4. Haematemesis and malena

Dentistry and Drugs Affecting Coagulation

Most dental procedures including minor ones like scaling and tooth extraction involves some amount of bleeding. In patients with normal haemostasis, this is not much of a problem as bleeding stops by itself. However, even minor dental procedures may result in continuous bleeding from the site in the following patients—

- Patients receiving drugs that inhibit coagulation.
 - Thrombocytopenic purpura
 - Vitamin C deficiency
 - Haemophiliacs
 - Long-term glucocorticoid therapy.
- For management of bleeding—See page 399

HYPOLIPIDAEMIC DRUGS

Lipids and proteins form complexes called lipoproteins and circulate in the blood vessels. There are four types of lipoproteins-

- Low density lipoproteins (LDL)
- High density lipoproteins (HDL)
- Very low density lipoproteins (VLDL)
- Chylomicrons.

LDL is the primary carrier of cholesterol while VLDL carry triglycerides. Hyperlipoproteinaemias (HPL) are conditions in which the concentration of cholesterol or triglyceride (TG) carrying lipoproteins in the plasma is elevated above normal (Table 33.4). Increase in lipoproteins can hasten the development of atherosclerosis and is a risk factor for myocardial infarction. Therefore, along with reduction of body weight and low cholesterol diet, significant hyperlipoproteinaemias should be treated with hypolipidaemic drugs. It should be noted that HDL is known to have antiatherogenic effects. Low levels of HDL can increase the risk of atherosclerosis. It is therefore desirable to have higher HDL levels with low LDL and TG levels.

HYPOLIPIDAEMICS1. *HMG CoA reductase inhibitors* —

Lovastatin
Simvastatin
Pravastatin
Atorvastatin

2. *Fibric acids* —

Gemfibrozil
Clofibrate
Fenofibrate
Bezafibrate
Ciprofibrate

3. *Bile acid binding resins*—

Cholestyramine
Colestipol

4. *Antioxidant* —

Probucol

5. *Miscellaneous* —

Nicotinic acid
Neomycin
Gugulipid

HMG CoA Reductase Inhibitors (Statins)

Hydroxymethylglutaryl-CoA (HMG-CoA) is the rate-controlling enzyme in the biosynthesis of cholesterol. Lovastatin and its congeners are competitive inhibitors of the enzyme HMG-CoA. They lower plasma LDL cholesterol and triglycerides. The concentration of HDL-cholesterol (the protective lipoprotein) increases by 10%.

Pharmacokinetics Statins are well absorbed when given orally but may undergo extensive first pass metabolism in the liver. Food enhances their absorption. Simvastatin is a prodrug converted to its active metabolite in the liver.

Adverse effects include GI disturbances, headache, insomnia, rashes, and rarely angio-oedema. Statins can rarely cause muscle tenderness and myopathy with inflammation of the skeletal muscles causing muscle pain and weakness.

Uses

1. Several large scale studies have shown statins to be useful in lowering morbidity and mortality in patients with coronary heart disease. Hence they are used in patients with MI, angina, stroke and transient ischemic attacks to lower cholesterol levels.
2. HMG CoA reductase inhibitors are the first line drugs for hyperlipidaemias (Table 33.5) both for familial and secondary hyperlipidaemias as in diabetes mellitus.

Fibric Acids (Fibrates)

Fibric acids enhance activity of the enzyme lipoprotein lipase which degrades VLDL resulting in lowering of triglycerides. They also increase HDL levels.

Table 33.4: Plasma lipid levels (mg/dl)

Grade	Total cholesterol	LDL	Triglycerides	HDL
Normal	< 200	< 130	< 150	> 40
Borderline	200-240	130-160	150-199	–
High	> 240	> 160	> 200	> 60

Fibrates also inhibit coagulation and promote thrombolysis which also account for their beneficial effects. Gemfibrozil 600 mg BD is the drug of choice in patients with increased TG levels and in type III, type IV and type V hyperlipoproteinaemias.

Adverse effects GI upset, skin rashes, headache, myositis, muscle cramps and blurred vision. Fibrates can cause rhabdomyolysis particularly in patients with renal failure.

Bezafibrate is similar to gemfibrozil and has greater LDL lowering effects.

Bile Acid Binding Resins

Bile acid binding resins—are not absorbed but they bind bile acids in the intestine and increase their excretion. Bile acids are required for intestinal absorption of cholesterol. Plasma cholesterol and LDL levels fall. Bile acid binding resins are unpleasant to take; they may cause GI upset, constipation and piles. They also bind fat soluble vitamins and many drugs like

warfarin, chlorothiazide digoxin in the intestines thereby reducing their absorption.

Bile acid binding resins can be used in patients with raised LDL levels; they can be used along with lovastatin or nicotinic acid.

Antioxidant

Probucol lowers LDL and HDL cholesterol and has antioxidant properties. It is generally not preferred.

Miscellaneous

Nicotinic acid—a B group vitamin, in large doses inhibits triglyceride synthesis in the liver and VLDL production resulting in a decrease in LDL and increase in HDL cholesterol. Adverse effects include flushing, dyspepsia, dryness and pigmentation of the skin.

Niacin is used in hypertriglyceridaemia with low HDL levels.

Gugulipid obtained from 'gum guggul' lowers plasma cholesterol and triglycerides. It is well tolerated but can cause diarrhoea.

Table 33.5: Choice of hypolipidaemics

↑ TG	Gemfibrozil
↑ LDL	Lovastatin* + cholestyramine/nicotinic acid
↑ TG+ ↑ LDL	Lovastatin* + Gemfibrozil

* or any other statin

Section 9

Gastrointestinal Tract

34

Drugs Used in Gastrointestinal Disorders

DRUGS USED IN PEPTIC ULCER

Acid-peptic disease is common in the present days that are full of tension and anxiety. Peptic ulcer is thought to result from an imbalance between acid-pepsin secretion and mucosal defense factors. The stomach secretes about 2.5 litres of gastric juice daily. The chief cells secrete pepsinogen while the parietal cells secrete HCl and intrinsic factor.

Gastric acid secretion is regulated by three pathways—vagus (through acetylcholine), gastrin and local release of histamine—each acting through its own receptors (Fig. 34.1). These activate $H^+ K^+ ATPase$ (proton pump) on the parietal cells resulting in the secretion of H^+ into the gastric lumen where it combines

with Cl^- (drawn from plasma) and HCl is secreted. Acetylcholine and gastrin act both directly on the parietal cells and indirectly by releasing histamine from the enterochromaffin cells. Histamine acts through H_2 receptors on parietal cells while acetylcholine through M_1 muscarinic and gastrin through G receptors.

The factors that protect the mucosa are its ability to secrete mucous, bicarbonate and prostaglandins. The mucous and bicarbonate form a layer which protects the gastric mucosa from gastric acid. Prostaglandins (PGE_2 & I_2) stimulate the secretion of mucus and bicarbonate, bring about vasodilation and also inhibit acid secretion. They act on the PG receptors present on the parietal cell.

CLASSIFICATION

Drugs used in peptic ulcer may be classified as follows:

- | | |
|--|---|
| 1. <i>Drugs that neutralise gastric acid</i> | - <i>Antacids</i> - Magnesium hydroxide, aluminium hydroxide, calcium carbonate, sodium bicarbonate |
| 2. <i>Drugs that reduce gastric acid secretion</i> | |
| a. H_2 receptor blockers | - Cimetidine, ranitidine, famotidine, roxatidine, nizatidine |
| b. Proton pump inhibitors | - Omeprazole, lansoprazole, esomeprazole, pantoprazole, rabeprazole |
| c. Muscarinic antagonists | - Pirenzepine, telenzepine |
| 3. <i>Ulcer protectives</i> | - Sucralfate, bismuth compounds |
| 4. <i>Other drugs</i> | - Carbenoxolone, cisapride, prostaglandins. |

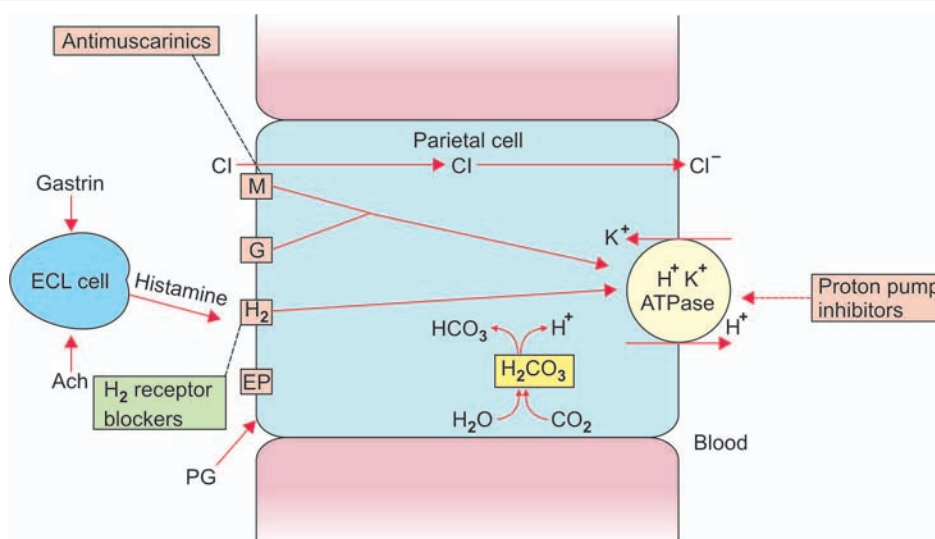


Fig. 34.1: Regulation of gastric secretion: ECL–Enterochromaffin cell; M–Muscarinic receptor (chiefly M_1); G–Gastrin receptors; H_2 –Histamine H_2 receptor

The exact aetiopathogenesis of peptic ulcer is not known. Infection of the stomach mucosa with *Helicobacter pylori* is now known to be associated with chronic gastritis, peptic ulcers and their recurrence.

ANTACIDS

Antacids are basic substances. Given orally they neutralize the gastric acid and raise the pH of gastric contents. Peptic activity is also reduced, as pepsin is active only below pH 4. Antacids are of 2 types:

1. *Systemic* Sodium bicarbonate
2. *Non-systemic* Aluminium hydroxide, Magnesium trisilicate, Magnesium hydroxide, Calcium carbonate.

Systemic Antacids

Sodium bicarbonate is rapid but short-acting. CO_2 that is released in the stomach escapes as eructation. It gets absorbed from the

intestines leading to systemic alkalosis. There is 'rebound' hyperacidity as gastrin levels increase due to raised gastric pH. Sodium load may increase. It is not preferred for long-term use because of the above disadvantages.

Sodium bicarbonate is used with other antacids in peptic ulcer. Other uses are to alkalinise the urine in poisoning due to certain drugs and to treat metabolic acidosis.

Non-systemic Antacids

Non-systemic antacids are insoluble compounds that react in the stomach with HCl to form a chloride salt and water. They are not absorbed.

Aluminium hydroxide is slow acting. Food further slows its neutralizing capacity. It is also an astringent and demulcent–forms a protective coating over the ulcers. The aluminium ions relax the smooth muscles resulting in delayed gastric emptying and constipation. Aluminium hydroxide binds phosphate and prevents its absorption resulting in hypophosphataemia on prolonged use.

Magnesium salts The action is quick and prolonged. Rebound acidity is mild. Magnesium salts are osmotic purgatives and the dose used as antacids may cause mild diarrhoea.

Calcium carbonate acts quickly and has prolonged action but liberates CO_2 which may cause discomfort. It may also cause constipation and hypercalcaemia.

Antacid combinations are given to obtain maximum effects with least adverse effects as follows (Table 34.1)-

1. **Quick and prolonged effect**—Fast-acting $[\text{Mg}(\text{OH})_2]$ and slow as well as long acting $[\text{Al}(\text{OH})_3]$ compounds are combined
2. **Neutralising side effects**—Magnesium salts have a laxative effect while aluminium salts are constipating—combination neutralises each others side effects.
3. **Gastric emptying**—Magnesium salts hasten while aluminium salts delay gastric emptying.
4. **Additive effect**—The acid neutralising effects of both salts get added up.

All antacid tablets should be chewed and swallowed as they do not disintegrate well in the stomach. Gels are more effective than tablets. One dose given 1 hr after food neutralises the acid for 2 hours.

Uses

Antacids are used as adjuvants in hyperacidity, peptic ulcer and reflux oesophagitis.

Drug Interactions

Antacids form complexes with iron, tetracyclines, digoxin, ranitidine, fluoroquinolones, sulfonamides and antimuscarinic drugs. To avoid these, antacids should be taken 2 hours before or 2 hours after other drugs.

H_2 RECEPTOR BLOCKERS

Cimetidine, ranitidine, famotidine, roxatidine, nizatidine.

These drugs competitively inhibit the action of histamine on H_2 receptors (Table 34.2) and thereby reduce gastric secretion. Both volume and acidity of basal, nocturnal and food induced secretion are reduced. They can cause 90% reduction in gastric secretion by a single dose. Gastrin induced HCl secretion and pepsin is also reduced. These actions, particularly their ability to suppress nocturnal acid secretion, hasten the healing of peptic ulcers.

Pharmacokinetics H_2 blockers are rapidly and well-absorbed. Cimetidine acts for 5-8 hours, ranitidine and famotidine for 12 hours. They are partly metabolised in the liver and excreted by the kidneys. Dose - Table 34.3.

Adverse effects The H_2 blockers are well-tolerated with minor side effects like diarrhoea, dizziness, muscle pain and headache.

Table 34.1: Some antacid combination preparations

Brand name	Combination
1. GELUSIL liquid	Aluminium hydroxide gel 312 mg + Magnesium trisilicate 625 mg in every 5 ml
2. GELUSIL tablet	Aluminium hydroxide gel 250 mg + Magnesium trisilicate 500 mg
3. DIGENE gel	Magnesium hydroxide 185 mg + Aluminium hydroxide gel 830 mg + Carboxymethyl cellulose sodium 100 mg + Methylpolysiloxane 25 mg—in every 10 ml
4. DIGENE tablet	Dried aluminium hydroxide gel 30 mg + Magnesium silicate 50 mg + Magnesium hydroxide 25 mg+Methylpolysiloxane 10 mg

Table 34.2: Compare and contrast promethazine (H_1 blocker) and ranitidine (H_2 blocker)

Features	Promethazine	Ranitidine
Antagonist of	Histamine	Histamine
Subtype of receptor blocked	H_1	H_2
Other receptors blocked	M_1 Muscarinic	Nil
Effect on sleep	Sedative	No sedation
Anticholinergic effects	Present	Absent
Gastric HCl secretion	Not affected	Decreased
Antiemetic property	Present	Absent
Primary use	Allergic disorders	Acid peptic disease
CNS effects of alcohol	Potentiated	No effect

Cimetidine has antiandrogenic actions, it increases plasma prolactin levels and inhibits oestrogen metabolism in the liver. On prolonged use it may result in gynaecomastia, decreased sperm count, impotence and loss of libido in men. CNS effects include confusion, delirium and hallucinations in the elderly. Headache, dizziness, rashes and diarrhoea can result. *Cimetidine* inhibits microsomal enzymes (cytochrome P_{450}) and interferes with the metabolism of many drugs. *Ranitidine* is the preferred H_2 blocker as it has several advantages over *cimetidine*. *Ranitidine* is more potent, longer acting, has no antiandrogenic effects, no CNS effects as it does not cross the BBB and does not inhibit microsomal enzymes significantly. Only adverse effects are headache and dizziness. *Famotidine* is similar to but more potent than *ranitidine*. Headache and rashes can occur. *Roxatidine* is similar to *ranitidine* but is more potent and longer-acting.

Uses of H_2 Blockers

H_2 blockers are used in the treatment of peptic ulcer, gastritis, reflux oesophagitis (GERD) and as preanaesthetic medication—to prevent damage to the respiratory mucosa if

aspiration occurs during surgery (See Page 139). *Ranitidine* is the most preferred. It is given for 4-8 weeks in peptic ulcers. It may be continued for 6 months to prevent recurrence.

PROTON PUMP INHIBITORS

Proton pump (PP) inhibitors are the most efficacious inhibitors of the gastric acid secretion. *Omeprazole* was the first to be developed but we now have *lansoprazole*, *pantoprazole* and *rabeprazole* with minor pharmacokinetic variations.

Omeprazole is the most commonly used PP inhibitor.

Mechanism of Action

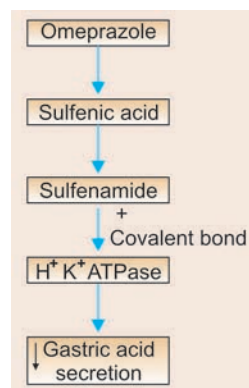


Table 34.3: Dosage and frequency of administration of drugs used in peptic ulcer

Drug	Dose and frequency
Ranitidine (RANTAC)	150 mg BD/300 mg HS
Famotidine (FAMOTIN)	20 mg BD/40 mg HS
Roxatidine (ROTANE)	75 mg BD/150 mg HS
Cimetidine (CIMET)	400 mg BD/800 mg HS
Omeprazole (OMEZ, LOMAC)	20-40 mg OD
Lansoprazole (LANZOL)	15-30 mg OD
Rabeprazole (VELOZ)	20 mg OD
Sucralfate (SUCRACE)	1 g 1 hr before each meal
Colloidal bismuth subcitrate (PYLOCID)	120 mg 1 hr before meals and at bed time
Carbenoxolone (GASTRIULCER)	50-100 mg TDS
Misoprostol	200 mg BD-QID

The parietal cells of the stomach secrete H^+ with the help of an enzyme H^+K^+ ATPase (proton pump) present in the plasma membrane. This is the final step in gastric acid secretion due to all stimuli. Proton pump inhibitors accumulate in the parietal cells where they specifically and irreversibly inhibit H^+K^+ ATPase and thereby inhibit gastric secretion. Omeprazole and other proton pump inhibitors are prodrugs, get activated in the acidic environment of the stomach to sulfenamide which binds covalently with (SH groups on) H^+K^+ ATPase. The binding is irreversible. A single dose can almost totally (95%) inhibit gastric secretion. Acid secretion starts only after new H^+K^+ ATPase enzyme is synthesized. Ulcer heals rapidly even in resistant cases.

Pharmacokinetics PP inhibitors are given as enteric coated granules to avoid degradation by the acid in the stomach. Omeprazole is rapidly absorbed and reaches the parietal cells; it is highly protein bound and is metabolised in the liver by the microsomal enzymes (cytochrome P450). Though the $t_{1/2}$ of omeprazole is 1-2 hours, the effect of a single dose remains for 2-3 days because of its accumulation in the parietal cell canaliculi.

PP inhibitors are microsomal enzyme inhibitors and can result in many drug interactions—they may enhance the plasma levels of drugs like benzodiazepines, warfarin and phenytoin—precipitating toxicity.

Adverse effects Omeprazole is well-tolerated. Prolonged acid suppression may allow bacterial over growth in the stomach. Dizziness, headache, diarrhoea, abdominal pain, nausea, arthralgia and rashes are rare. Long-term administration may result in—

- Vitamin B₁₂ deficiency due to its reduced absorption.
- ↑Gastrin levels.
- Atrophic changes in the stomach have been noticed after 3-4 years of use.

Drug Interactions

- Antacids, H_2 receptor blockers and other drugs which reduce gastric acidity reduce the efficacy of proton pump inhibitors.
- PP inhibitors inhibit the microsomal enzyme activity which can result in many drug interactions.

Lansoprazole is similar to omeprazole but is longer-acting.

Pantoprazole is more acid stable and an intravenous formulation is also available for use. It does not inhibit microsomal enzymes. All other features are similar to omeprazole. *Rabeprazole* is shorter acting.

Uses of PP Inhibitors

- Proton pump inhibitors are used in peptic ulcers and in severe gastroesophageal reflux disease that does not respond to H_2 blockers. Ulcers heal fast and pain is relieved. They are given for 4-8 weeks.
- They also form a component in *H. pylori* treatment regimen.
- PP inhibitors are useful in Zollinger Ellison syndrome associated with gastrin secreting tumours.

Anticholinergics Though atropine reduces gastric secretion, the dose needed results in several adverse effects. A derivative of atropine—pirenzepine selectively blocks gastric M_1 receptors and inhibits gastric secretion by 40-50% without significant side effects. It also inhibits the secretion of gastrin, mucous and bicarbonate. It is used as an adjuvant.

Ulcer Protectives

Sucralfate In acidic medium ($pH < 4$), sucralfate polymerises to form a sticky, viscid gel which firmly adheres to the base of the ulcers. It remains there for over 6 hours acting as a physical barrier and prevents contact with acid and pepsin. It also stimulates the PG synthesis in gastric mucosa. It thus promotes healing by protecting the ulcer. Sucralfate is not absorbed and is well-tolerated.

One tablet is given 1 hr before each meal and one at bed time for 4-8 weeks and then

1 gram BD is continued for 6 months to prevent recurrence.

Side effects are rare and include constipation and dryness of mouth.

Drug Interactions

- Sucralfate needs acidic pH for activation. Hence antacids should not be given with it.
- Sucralfate absorbs and interferes with the absorption of tetracyclines, digoxin, phenytoin and cimetidine.

Bismuth salts Colloidal bismuth subcitrate on oral administration chelates proteins in the ulcer base and forms a protective coating over the gastric mucosa. It also inhibits the growth of *H. pylori* on gastric mucosa and stimulates the mucus production and PG synthesis. By these actions it promotes ulcer healing in 4-8 weeks. It may cause constipation and black stools.

Other Drugs

Carbenoxolone is a steroid like compound obtained from glycyrrhizic acid found in the root of liquorice. On ingestion, it alters the composition of mucus so that it is more viscid and adheres to gastric mucosa and protects the ulcer base. It also inhibits pepsin activity and prolongs the life of PGs. Because of its steroid like effects, it causes salt and water retention. It is therefore not preferred.

Prostaglandins PGE_2 and PGI_2 synthesized by the gastric mucosa inhibits gastric secretion, enhances mucus production as well as mucosal blood flow and exert a cytoprotective effect. They act by binding to the PG receptor (EP_3) present on the parietal cells and inhibit cAMP production. **Misoprotol** is a synthetic PGE_1 analog given orally. It is of special value in preventing NSAID induced gastric ulceration because NSAIDs are PG synthesis inhibitors. Diarrhoea and muscle cramps are common.

Treatment of *H. pylori* Infection

The gram-negative bacterium *H. pylori* is adapted to living in the stomach. Infection with *H. pylori* is associated with gastro-duodenal disease including gastritis and peptic ulcer. It is also thought to be responsible for recurrence of peptic ulcer disease and is considered as a major risk factor for stomach cancer. Eradication of *H. pylori* along with drugs that reduce acid secretion has shown to reduce the relapse rate.

Various combination regimens are tried with clarithromycin, amoxicillin or tetracycline; metronidazole and omeprazole or a H_2 receptor blocker for 1-2 weeks. Use of a PP inhibitor in the regimen improves the efficacy of the antibiotics in eradicating *H. Pylori* by raising gastric pH and enhancing antibiotic stability - activity of amoxicillin and clarithromycin are pH dependent. Some regimens are:

1. Clarithromycin 250 mg BD + metronidazole 400 mg BD + omeprazole 20 mg BD—for one week.
2. Clarithromycin 500 mg TDS/amoxicillin 750 mg TDS + omeprazole 20 mg BD—for two weeks.

Relevance in Dentistry

Many drugs used by dentists particularly NSAIDs, can cause gastric irritation of varying degree. Dentists should be careful in using NSAIDs and other gastric irritant drugs including some antibiotics like doxycycline, ciprofloxacin, etc. in patients suffering from acid peptic disease. Though prophylactic ranitidine/omeprazole has been commonly prescribed with ulcerogenic drugs, routine use of such drugs is not recommended.

PROKINETIC AGENTS

Drugs that enhance gastroduodenal motility and hasten gastric emptying are called

prokinetic agents. Metoclopramide, domperidone and cisapride are some prokinetic agents.

Metoclopramide

Actions

GIT—Metoclopramide promotes forward movement of contents of the upper GI tract. It raises lower esophageal sphincter pressure, speeds up gastric emptying, prevents reflux esophagitis and also slightly enhances intestinal peristalsis.

CNS— Metoclopramide acts as an antiemetic by its actions on CTZ and by speeding up gastric emptying.

Mechanism of Action

Prokinetics act:

- (i) by blocking D_2 dopamine receptors. Antiemetic action is due to blockade of D_2 receptors in the CTZ.
- (ii) by enhancing acetylcholine release from the cholinergic neurons in the gut.

Adverse effects are sedation, dystonia and diarrhoea; gynaecomastia, galactorrhoea and parkinsonism (extrapyramidal symptoms) can occur on long-term use.

Uses

1. Reflux oesophagitis—'heart burn' due to reflux of acid into the oesophagus is benefited by prokinetic agents.
2. As antiemetics – in postoperative period and vomiting due to anticancer drugs.
3. As preanaesthetic medication to promote gastric emptying before induction of general anaesthesia in emergency.
4. In endoscopy—to assist passage of tubes into the duodenum.

Domperidone is a D_2 dopamine receptor blocker like metoclopramide. It does not cross the blood-brain barrier and hence extrapyramidal

side effects are rare. As CTZ is outside the BBB, it acts as an antiemetic. Side effects are rare and include headache, dryness of mouth, diarrhoea and rashes.

Domperidone can be used in place of metoclopramide.

Cisapride enhances gastric motility by promoting the release of acetylcholine in the gut wall. It does not block dopamine receptors—hence is not an antiemetic and there are no antidopaminergic side effects. It also promotes colonic motility which may result in diarrhoea. It was used in reflux oesophagitis. *Cisapride* is now banned because it can cause serious cardiac adverse effects. Cardiac arrhythmias including ventricular tachycardia, and atrial fibrillation can occur—particularly when used with microsomal enzyme inhibitors like erythromycin, fluconazole, ketoconazole, indinavir and ritonavir.

Tegaserod is a 5HT₄ partial agonist which promotes gastric emptying. It is free of the drug interactions and cardiotoxicity seen with *cisapride*.

Gastroesophageal reflux disease (GERD)
Reflux of acidic gastric contents into the oesophagus results in 'heart burn' due to oesophagitis. Chronic oesophagitis can result in changes in the esophageal mucosa which could be a premalignant condition. Based on severity, GERD may be treated with antacids, metoclopramide or drugs that reduce acid secretion. Uncomplicated, mild GERD may be relieved with antacids, H₂ receptor blockers or prokinetic agents. In moderate to severe cases, proton pump inhibitors like omeprazole are the drugs of choice. They effectively relieve symptoms and promote the healing of oesophagitis in 4-8 weeks. Avoiding—heavy meals, late night dinner, smoking and alcohol—all help.

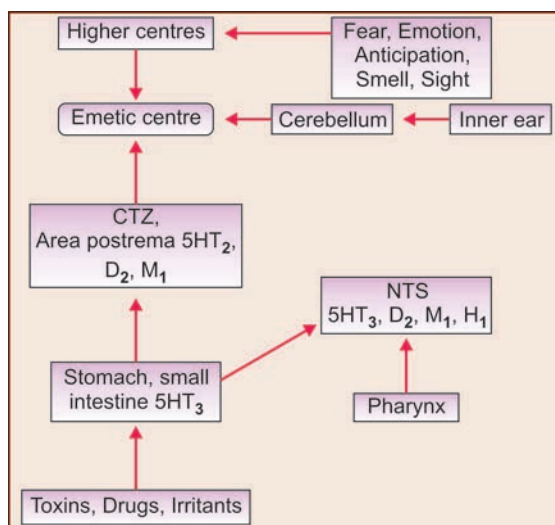


Fig. 34.2 : The stimuli, pathways and centres mediating emetic reflex

EMETICS AND ANTIEMETICS

Stimulation of the vomiting centre in the medulla oblongata results in vomiting. The vomiting centre receives afferents from the chemoreceptor trigger zone (CTZ), vestibular apparatus, GI tract and centres in the brain (Fig. 34.2). CTZ is not protected by the blood-brain barrier and is stimulated by various drugs, chemicals and radiation.

Emetics are drugs that produce vomiting. When a noxious substance is ingested, vomiting has to be induced. Mustard powder (1 teaspoon) with water or hypertonic salt solution can evoke vomiting.

Apomorphine is a derivative of morphine. Given SC/IM, it produces vomiting in 5-10 minutes. It acts by stimulating the CTZ.

Ipecacuanha contains an alkaloid emetine. Given as a syrup (15- 20 ml), it produces vomiting in 15 minutes. It is safe even in children.

Antiemetics

Vomiting is a protective mechanism aimed at eliminating the unwanted harmful

material from the stomach. But in some situations, vomiting may not serve any useful purpose and may only be troublesome. It can cause dehydration, weakness and electrolyte imbalance. In such circumstances, vomiting needs to be suppressed with drugs.

CLASSIFICATION

1. *Dopamine D₂ antagonists–prokinetics* -
Metoclopramide, domperidone
2. *5HT₃ antagonists*
Ondansetron, granisetron
dolasetron, tropisetron
3. *Antimuscarinics*
Hyoscine
cyclizine
promethazine
diphenhydramine. } H₁ anti-histamines
4. *Neuroleptics*
Chlorpromazine,
prochlorperazine, haloperidol
5. *Other agents*
Cisapride, corticosteroids.

Dopamine D₂ Antagonists

Metoclopramide and *domperidone* (page 243) act centrally by blocking dopamine D₂ receptors in the CTZ. They enhance the tone of the lower oesophageal sphincter and also enhance gastric peristalsis. They are used in nausea and vomiting due to gastrointestinal disorders, migraine, in postoperative period and vomiting due to cytotoxic drugs and radiotherapy.

5-HT₃ Antagonists

Ondansetron 5-hydroxytryptamine released in the gut is an important transmitter of emesis. It is believed that anticancer drugs induce the release of 5-HT in the gut which initiates emetic reflex through 5-HT₃ receptors present

in the gut, NTS and area postrema. *Ondansetron* blocks 5-HT₃ receptors in the GI tract, CTZ and nucleus tractus solitarius and prevents vomiting. It is a powerful antiemetic and can be given orally or intravenously (4-8 mg).

5-HT₃ antagonists

- Block 5-HT₃ receptors in the gut, CTZ and NTS.
- Efficient antiemetics.
- Some are effective both orally and parenterally.
- Largely safe – no sedation or other CNS/autonomic side effects.
- Adverse effects negligible – headache, gastrointestinal disturbances.
- Drugs of choice in postoperative and anticancer drug-induced vomiting.

Granisetron is more potent than *ondansetron* as an antiemetic. Though *granisetron*, *dolasetron* and *tropisetron* have longer t_{1/2}, their biological effect half-life remains the same and they can all be given once daily.

5HT₃ antagonists are well absorbed from the gut and are metabolised by the liver. They can be given both orally, IM and IV.

All 5HT₃ antagonists are well tolerated with minor adverse effects like headache and constipation.

Uses

5HT₃ antagonists are used to control vomiting induced by anticancer drugs or radiotherapy. They are also useful in postoperative vomiting and other drug induced vomiting (Table 34.4).

Antimuscarinics

Hyoscine (see Chap. 8) is a labyrinthine sedative very effective in motion sickness. Motion sickness or travelling sickness is due

to over stimulation of the vestibular apparatus along with psychological and environmental factors. Hyoscine also relaxes the gastrointestinal smooth muscle. Taken 30 minutes before journey, hyoscine (0.4-0.6 mg oral) acts for 6 hours and the dose should be repeated if the journey is longer than that. A transdermal patch delivers hyoscine constantly over 3 days and is to be applied behind the ear. Sedation and dry mouth are common side effects.

Dicyclomine is used to control vomiting in morning sickness and motion sickness (Table 34.3).

H₁ antihistamines (see Chap. 31) like promethazine, diphenhydramine, cyclizine and cinnarizine have anticholinergic properties. Antihistamines block H₁ receptors in the area postrema as well as muscarinic receptors in the CNS. They probably also act on the GI tract. Some of them are useful in motion sickness and postoperative vomiting. *Neuroleptics* (Chap. 29) also block D₂-receptors in the CTZ and are useful in vomiting due to most causes except motion sickness. Sedation and extrapyramidal symptoms are the common side effects. Prochlorperazine is mainly used as an antiemetic in vomiting and is also effective in vertigo associated with vomiting.

Other Antiemetics

Corticosteroids are used in combination with other antiemetics like ondansetron or metoclopramide. Corticosteroids control delayed vomiting following anticancer drug therapy.

Pyridoxine is used in the prevention of vomiting in pregnancy without any known pharmacological basis

Sedative hypnotics—Barbiturates and benzodiazepines may raise the threshold for vomiting by depressing the CNS. Their anxiolytic and sedative properties also help. Sedative hypnotics are used as adjuvants to other antiemetics in treating anticancer drug-induced vomiting.

Cannabinoids—Dronabinol, a cannabinoid has antiemetic properties. It may act by the stimulation of the cannabinoid receptors (CB₁) in the vomiting centre. It also increases appetite. Dronabinol can cause behavioural abnormalities and dependence. It can be used as an alternative in the prevention of vomiting when other drugs are ineffective.

Antiemetic Combinations

Severe retching and vomiting like that induced by anticancer drugs are treated with a combination of antiemetics including

Table 34.4: Preferred drugs for vomiting due to various causes

Conditions	Drugs
Motion sickness	Hyoscine, Cyclizine, Promethazine, Cinnarizine
Vomiting due to cytotoxic drugs	1. Ondansetron + Dexamethasone 2. Metoclopramide + dexamethasone + diphenhydramine+ lorazepam
Vomiting due to other drugs	Chlorpromazine, Metoclopramide
Postoperative vomiting	Ondansetron, Metoclopramide
Vomiting in pregnancy	Dicyclomine, Pyridoxine, Cyclizine, Meclizine, Metoclopramide

ondansetron, metoclopramide, glucocorticoids and sedative-hypnotics.

Later cycles of anticancer drug regimens can cause 'anticipatory' vomiting *i.e.* vomiting at the sight/thought of receiving anticancer drugs. This can be avoided by using appropriate antiemetics from the initial cycles of anticancer therapy.

DRUGS USED IN THE TREATMENT OF CONSTIPATION

Purgatives are drugs that promote defecation. They are also called *laxatives* or *cathartics*. *Laxatives* have milder action while cathartics or purgatives are more powerful evacuants. Purgatives may be classified as-

CLASSIFICATION

1. *Bulk laxatives*
Bran, plantago seeds, agar, methylcellulose, ispaghula husk
2. *Faecal softeners*
Docusate sodium, liquid paraffin (emollients)
3. *Osmotic purgatives*
Magnesium sulphate, Magnesium hydroxide, Sodium phosphate, Sodium sulphate, Magnesium citrate, Lactulose, Sorbitol, Polyethylene glycol
4. *Stimulant purgatives*
Phenolphthalein, bisacodyl, castor oil, Anthraquinones - cascara sagrada, senna

Bulk laxatives include indigestible vegetable fibre and hydrophilic colloids that increase the volume and lower the viscosity of intestinal contents forming a large, soft, solid stool. Dietary fibre consists of cell walls and other parts of fruits and vegetables that are unabsorbable. Adding fibre to the diet is a safe and natural way of treating constipation in persons on low-fibre diet.

Bran is the residue left when flour is made from cereals and contains 40% fibre—but is unpalatable and can cause flatulence. Ispaghula and plantago seeds contain natural mucilage which absorbs water to form a gelatinous mass and are more palatable than bran. Methylcellulose is a semisynthetic derivative of cellulose. Adequate water intake should be stressed.

Faecal Softeners

Docusate sodium (dioctyl sodium sulphosuccinate) softens faeces by lowering the surface tension of the intestinal contents which allows more water to be retained in the faeces.

Liquid paraffin is a chemically inert mineral oil that is not digested. It lubricates and softens faeces. It is unpalatable; aspiration may cause lipoid pneumonia; small amounts absorbed in intestines may cause parafinomas; it may leak out of the anus causing discomfort. Long-term use can result in deficiency of fat - soluble vitamins due to impaired absorption. Hence not preferred.

Osmotic Purgatives

Osmotic purgatives are solutes that are not absorbed in the intestine, osmotically retain water and increase the bulk of intestinal contents. They increase peristalsis to evacuate a fluid stool. They produce soft liquid stools in 1-3 hours. Osmotic purgatives include

- nonabsorbable salts (saline purgatives)
- nonabsorbable sugars - Lactulose
- polyethylene glycol

Nonabsorbable salts Magnesium hydroxide, magnesium sulphate, sodium potassium tartrate (Rochelle's salt), sodium sulphate and phosphate are some inorganic salts used as osmotic or *saline purgatives*. They are used to prepare the bowel before surgery and in food poisoning.

Nonabsorbable sugars Lactulose is a synthetic disaccharide that is not absorbed, holds water and acts as an osmotic purgative. Flatulence and cramps may be accompanied. In the colon, lactulose is fermented to lactic and acetic acids which inhibit the growth of colonic ammonia - producing bacteria. It also inhibits the absorption of ammonia by lowering pH and lowers blood ammonia levels. It is used in hepatic coma for this effect (hepatic coma is worsened by ammonia).

Sorbitol is similar to lactulose

Polyethylene glycol (PEG) is a nonabsorbable sugar. Balanced isotonic solution containing PEG with sodium sulphate, sodium chloride, sodium bicarbonate and potassium chloride is given orally. The solution is balanced in such a way that it avoids electrolyte imbalance or fluid shift into the gut. Large volumes are rapidly ingested → 3-4 litres over 2 hours - for cleaning the bowel. PEG powder may be taken with water for chronic constipation. It has the advantage that there is no associated flatulence or abdominal cramps.

Stimulant Purgatives

Stimulant purgatives increase intestinal motility and increase secretion of water and electrolytes by the mucosa. They may cause abdominal cramps.

When anthraquinones like *cascara sagrada* and *senna* (source: plants) are given orally, active anthraquinones are liberated in the intestines and stimulate the myenteric plexes in the colon. Evacuation takes 6-8 hr. Long-term use causes melanotic pigmentation of the colon.

Phenolphthalein an indicator, acts on the colon after 6 to 8 hours to produce soft, semiliquid stools with some gripping. It undergoes enterohepatic circulation which prolongs its actions. Allergic reactions including pink

coloured skin eruptions, other severe forms of allergy and risk of cardiac toxicity and colic limit its use.

Bisacodyl related to phenolphthalein is converted to active metabolite in the intestines. It can be given orally (5 mg) but usually is used as rectal suppositories (10 mg) which results in defecation in 15-30 minutes. It is safe except that prolonged use may cause local inflammation.

Castor oil is hydrolysed in the upper small intestine to ricinoleic acid, a local irritant that increases intestinal motility. It is a powerful and one of the oldest purgatives. Stool is semiliquid and is accompanied by gripping. It is not preferred.

Enema Enema produces defecation by softening stools and distending the bowel. Evacuant enema is used to prepare the gut for surgery, endoscopy and radiological examination (see Page 8).

Use of laxatives in constipation Fibre rich diet, adequate fluid intake and physical activity are the best measures to prevent and treat constipation in the otherwise normal subjects. If these measures are inadequate, a laxative may be given (Table 34.5).

Drug induced constipation Drugs like anticholinergics, NSAIDs, opioids, clonidine, iron, calcium channel blockers; antihistamines and tricyclic antidepressants (due to anticholinergic effect) can cause constipation. When withdrawal of the causative agent is not possible, a laxative may be used.

Laxative abuse Habitual use of laxatives, especially stimulant laxatives may lead to various gastrointestinal disturbances like irritable bowel syndrome, loss of electrolytes, loss of calcium in the stool and malabsorption. Misconceptions regarding bowel habits should be cleared. The patient should be convinced that normal bowel habits may vary between 3 motions daily and 2 motions per week.

Table 34.5: Choice of purgatives

Conditions	Preferred laxative
1. Functional constipation	Increasing dietary fibre and adequate fluid intake
2. Elderly patients	Increasing dietary fibre and adequate fluid intake
3. Pregnancy	Dietary fibre
4. To avoid straining at stools—as in hernia, piles, fissure, cardiovascular diseases like myocardial infarction	Bulk laxatives or faecal softeners
5. Irritable bowel syndrome—chronic constipation	Bulk laxatives
6. Food or drug poisoning	Osmotic purgatives
7. Bowel preparation before surgery, endoscopy and radiological examination	Bisacodyl, osmotic purgatives

DRUGS USED IN THE TREATMENT OF DIARRHOEA

Diarrhoea is the frequent passage of liquid stools. It can be due to a variety of causes like infection, toxins, anxiety and drugs. Acute diarrhoea is one of the major causes of death in infants specially in the developing countries.

In diarrhoea, there is an increase in motility and secretions in the gut with decreased absorption of water and electrolytes. Hence the approaches in the treatment of diarrhoea include:

1. replacement of fluid and electrolytes
2. treatment of the cause
3. antidiarrhoeal agents.

Correction of fluid and electrolyte disturbances can be life saving in most cases especially infants. Oral rehydration with sodium chloride, glucose and water is useful. In the ileum, glucose and sodium citrate enhance sodium absorption and water follows. Oral rehydration powders are available (Table 34.6) to be mixed with water for mild to moderate cases. ORS with sodium bicarbonate and with sodium citrate are available. Trisodium citrate is used in place of bicarbonate because use of citrate makes ORS more stable, absorption of glucose is

Table 34.6: Composition of oral rehydration salt/solution (ORS)

Sodium chloride	—	3.5 gm
Potassium chloride	—	1.5 gm
Sodium citrate	—	2.9 gm
Glucose	—	20 gm
To be dissolved in 1 litre of boiled and cooled water		

better and stool output is lower. If the ORS powder is not available, a mixture of 5 g table salt with 20 g sugar dissolved in one litre of boiled and cooled water may be used till regular ORS is available. In severe degrees of dehydration, prompt intravenous rehydration is vital.

Treatment of the cause Acute diarrhoea could often be due to viral, bacterial or protozoal infection. The pathogen should be identified whenever possible and treated accordingly. Gastroenteritis is often due to virus and does not require antibiotics. Mild bacterial gastroenteritis is also self-limiting but some infections like typhoid, cholera and amoebic dysentery need chemotherapy.

Antidiarrhoeal drugs afford symptomatic relief and include *adsorbents* and antimotility drugs.

Adsorbents include kaolin, pectin, chalk and activated charcoal. Kaolin is a natural compound containing hydrated magnesium, aluminium silicate while pectin is the sugar obtained from apples. These adsorb intestinal toxins and microorganisms by coating them. They are not absorbed and have no prominent side effects. They bind to and interfere with the absorption of other drugs because of which a 2-hour interval is required after administration of other drugs.

Antimotility Drugs

Codeine an opium alkaloid, stimulates the opioid receptors on the gastrointestinal smooth muscles to reduce peristalsis. This delays passage of intestinal contents and facilitates absorption of water. Nausea and vomiting may occur.

Diphenoxylate is an opioid related to pethidine. It is given with a small dose of atropine in order to discourage abuse. In therapeutic doses CNS effects are not prominent and is used only in diarrhoeas. Nausea, drowsiness and abdominal pain may occur (Table 34.7).

Loperamide is an opiate. It has selective action on GI tract with additional antisecretory action. CNS effects are negligible. It is less sedating, less addicting and is the most commonly used antimotility drug. Its low solubility in water discourages abuse by injection. Loperamide may cause nausea, vomiting and abdominal cramps.

Pathogens commonly causing diarrhoea

Virus	Bacteria	Others
<i>Rotavirus</i>	<i>E. coli</i>	<i>E. histolytica</i>
<i>Astrovirus</i>	<i>Salmonella</i>	<i>Giardia lamblia</i>
<i>Adenovirus</i>	<i>Shigella</i>	Intestinal worms
<i>Coronavirus</i>	<i>V. cholerae</i>	
<i>Enterovirus</i>	<i>C. jejuni</i>	

Antimotility drugs are used for symptomatic treatment of non-infective diarrhoeas and traveller's diarrhoea (as adjuvant).

Other Drugs

Lactobacillus acidophilus is available as powders and tablets and is useful in some diarrhoeas. It promotes the growth of saccharolytic flora and alters the gut pH so that growth of pathogenic organisms is inhibited.

Antispasmodics Atropine derivatives like propantheline and dicyclomine relax gastrointestinal smooth muscles and relieve abdominal colics.

Octreotide is a synthetic analog of somatostatin. Somatostatin has the following actions:

- reduces GI motility and fluid secretion.
- inhibits the secretion of various hormones like gastrin, secretin, cholecystokinin, growth hormone, insulin, glucagon, 5-HT, pancreatic polypeptide and vasoactive intestinal peptide.

Octreotide is a longer acting analog and can be given subcutaneously. It is used in diarrhoea caused by gastrointestinal secretory

Table 34.7: Antimotility drugs—some preparations and dosage

Drugs	Trade names	Doses
Diphenoxylate 2.5 mg + Atropine 0.025 mg	LOMOTIL	2-4 tablets stat; 1 every 6 hr
Loperamide	LOPESTAL	4 mg stat; 2 mg every 6 hr

tumours and in diarrhoea due to vagotomy, dumping syndrome and AIDS.

Traveller's diarrhoea

Infection is the most common cause of traveller's diarrhoea and should be treated with suitable antimicrobials like doxycycline or ciprofloxacin. Oral rehydration salts and loperamide may also be used.

IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome (IBS) is a common condition characterised by abnormal bowel functions with no specific organic cause.

Diarrhoea or constipation with abdominal pain are seen. Causes could be stress, lack of dietary fibre, food allergy or emotional disturbances. When constipation is prominent, soluble dietary fiber like ispaghula is recommended and loperamide is preferred for diarrhoea. Benzodiazepines are given for the treatment of anxiety and other appropriate measures are taken depending on the symptoms and probable cause.

Newer drugs like alosetron and tegaserod which act on 5-HT receptors have been found to be useful in IBS.

General Considerations

INTRODUCTION

Chemotherapy can be defined as the use of chemicals in infectious diseases to destroy microorganisms without damaging the host tissues. *Antibiotics* are substances produced by microorganisms which suppress the growth of or destroy other microorganisms.

Pasteur and Joubert were the first to identify that microorganisms could destroy other microorganisms. Paul Ehrlich 'The father of Modern Chemotherapy' coined the term 'chemotherapy'. He showed that certain dyes can destroy microbes and demonstrated that methylene blue can be used in malaria. He also synthesised some arsenical compounds for the treatment of syphilis and sleeping sickness. Domagk in 1936 demonstrated that prontosil, a sulfonamide dye is effective in some infections. The production of penicillin for clinical use in 1941 marked the beginning of the 'golden era' of antibiotics. In the last 60 years, several powerful antibiotics and their semisynthetic derivatives have been produced.

Many infectious diseases which were earlier incurable can now be treated with just a few doses of antimicrobial drugs. Thus the development of antimicrobial drugs is one of the important advances of modern medicine. Infact antimicrobials are one of the most commonly prescribed drugs but are often the most over used or misused drugs.

CLASSIFICATION

Based on their *mechanisms of action*, anti-microbials are classified (Fig. 35.1) as follows.

Drugs that:

1. *Inhibit cell wall synthesis-*
Penicillins, cephalosporins, vancomycin, bacitracin, cycloserine.
2. *Damage cell membranes-*
-causing leakage of cell contents - Polymyxins, colistin, amphotericin B, nystatin.
3. *Bind to ribosomes and inhibit protein synthesis -*
Chloramphenicol, tetracyclines, erythromycin, aminoglycosides, clindamycin, linezolid, streptogramins.
4. *Inhibit DNA gyrase-*
Fluoroquinolones like ciprofloxacin, norfloxacin
5. *Inhibit DNA function-*
(DNA dependent RNA polymerase) Rifampicin
6. *Interfere with metabolic steps-*
-Antimetabolite action- sulfonamides, sulfones, trimethoprim, pyrimethamine

Antimicrobials may also be Classified as-

1. *Bacteriostatic* - agents that suppress the growth of bacteria.
For example, Sulfonamides, tetracyclines, linezolid chloramphenicol, clindamycin.

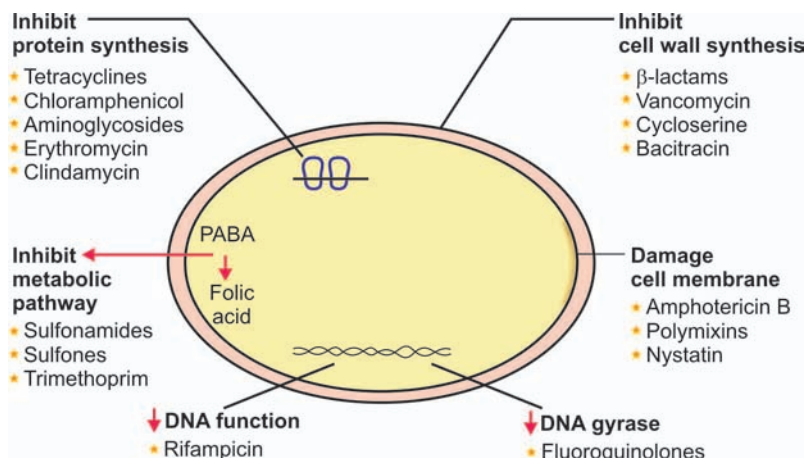


Fig. 35.1: Classification of antimicrobials based on their mechanisms of action

2. Bactericidal - agents that kill the bacteria.

For example, Penicillins, cephalosporins, aminoglycosides, fluoroquinolones, rifampicin, metronidazole, vancomycin.

However, some drugs may be bacteriostatic at low doses and bactericidal at higher doses. For example erythromycin; also, some drugs may be bacteriostatic to some microorganisms and 'cidal' to others. For example chloramphenicol is bactericidal to *H. influenzae*, *S. pneumoniae* and *N. meningitidis*, while it is bacteriostatic to other microorganisms.

Antibacterial spectrum An antimicrobial may have a narrow or broad spectrum of activity.

Narrow spectrum -

For example: Penicillin G - gram-positive

Aminoglycosides - gram-negative

Broad spectrum

- Tetracyclines,

- Chloramphenicol

Broad spectrum antibiotics are so called because, in addition to suppression of gram-positive and gram-negative bacteria, they also inhibit the growth of other microorganisms like Rickettsiae, Chlamydiae, Mycoplasma and some protozoa. But in practice the term 'broad spectrum' is often

used to include all antimicrobials with a wide spectrum of activity *i.e.* those effective against both gram-positive and gram-negative organisms *e.g.* ampicillin.

Factors that influence the successful chemotherapy of an infection are:

- **Site** The drug should reach the site of infection.
- **Concentration** It should attain adequate concentration at the site.
- **Host defence** Active host defences reduce the antibiotic requirement.
- **Sensitivity** The microorganism should be sensitive to the antimicrobial agent.

RESISTANCE TO ANTIMICROBIAL AGENTS

Resistance is the unresponsiveness of a microorganism to the antimicrobial agent. The resistance may be natural or acquired. In *natural resistance*, the organisms have never responded to the antimicrobial—may be due to the absence of the particular enzyme or target site affected by the drug, *e.g.* gram-negative bacilli are not sensitive to Penicillin G. But this type of resistance is clinically not a problem as alternative drugs are available.

Acquired resistance Here, the microbes which were previously sensitive to the antimicrobial agents become resistant to it. Clinically this poses a problem.

Bacteria acquire resistance by a change in their DNA. Such DNA changes may occur by: (i) *mutation* or (ii) *transfer of genes*.

Mutation is a genetic change that occurs spontaneously. In any population of bacteria, a few resistant mutants may be present. When the sensitive organisms are destroyed by the antibiotic, the resistant mutants freely multiply. Mutation may take place in a single step (e.g. *Staphylococcus aureus* to rifampicin) or multiple steps where several gene modifications are made, e.g. gonococci to penicillin G.

Transfer of genetic material Many bacteria contain extrachromosomal genetic material called *plasmids* in the cytoplasm. These carry genes coding for resistance (called R-factors). These R-factors are transferred to other bacteria and spread resistance (Fig. 35.2).

This may take place by:

1. **Transduction** Plasmid DNA is transferred through bacteriophage, i.e. virus which infects bacteria.

2. **Transformation** Resistant bacteria may release genetic material into the medium which is taken up by other bacteria.

3. **Conjugation** is the most important mode of spread of resistance. The R-factor is transferred from cell to cell by direct contact through a sex pilus or bridge and the process is known as conjugation.

The resistance acquired by the bacteria may be exhibited in the following ways:

- Production of enzymes that inactivate the drug, e.g. β -lactamase by staphylococci; aminoglycoside inactivating enzymes by *E.coli*.
- Decreased accumulation of the drug in the bacterium, e.g. resistance to tetracyclines by gram-positive and gram-negative bacteria.
- Altered target for the drug – the binding site may be altered, e.g. binding sites for aminoglycosides on the ribosomes may be altered.
- Altered metabolic pathway–bacteria may produce folic acid by an alternative pathway.

Cross resistance is the resistance seen among chemically related drugs. When a micro-organism develops resistance to one drug, it

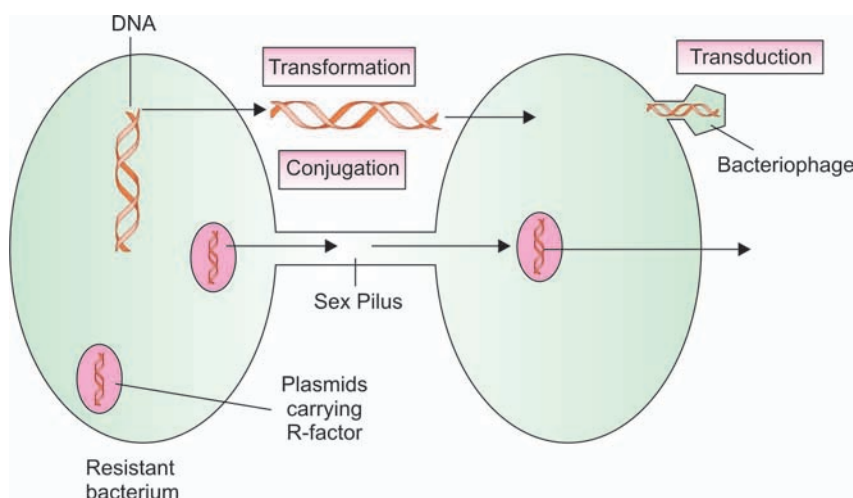


Fig. 35.2: Mechanisms of transfer of resistance

is also resistant to other drugs of the same group, even when not exposed to it, e.g. resistance to one tetracycline means resistance to all other tetracyclines.

Prevention of Resistance to Antimicrobials

Development of resistance to drugs can be avoided to some extent by the following measures:

- antibiotics should be used only when necessary
- selection of the appropriate antibiotic is absolutely important
- correct dose and duration of treatment should be followed
- combination of drugs should be used as in tuberculosis to delay the development of resistance.

Selection of an Antibacterial Agent

Antibiotics are used in 2 ways:

1. *Empiric therapy* The antibiotic must cover all the likely pathogens. A combination or a broad spectrum agent may be used. This therapy should be employed only in some specific situations.
2. *Definitive therapy* When the organism is identified, specific antibacterial agents should be given.

Various factors should be considered in selection of an antibiotic like, the patient factors, the microbe factors, the properties of the drug and the clinical assessment. Site of infection is the prime factor that guides the choice of the drug and its route of administration. Age of the patient, host defence status, renal and hepatic functions should be considered. Whenever possible, bacteriological culture report should guide the drug selection. When not available, empirical therapy should be started to cover all the likely organisms. Infact for most dental

infections, selection of an antibiotic is empirical. For acute dental infections the antibiotic should have a spectrum that includes streptococcal species and anaerobic bacteria. When samples can be taken without contamination or when empiric therapy fails, antibiotic selection should be based on culture report. Drug toxicity and cost should be borne in mind. With proper clinical judgement—considering the above factors, most infections can be successfully treated (Table 35.1).

DOSE OF THE ANTIMICROBIALS

The dose of the antimicrobial should be adequate enough for the drug to attain plasma concentrations above the *minimum inhibitory concentration* (MIC). MIC is the lowest concentration of the antimicrobial agent that prevents visible growth of the microorganism after 18 to 24 hours of incubation. The bactericidal effect with many drugs is dose-dependent i.e. higher the concentration, greater is the bactericidal effect, e.g. aminoglycosides.

Postantibiotic effect - Some antibiotics have a postantibiotic effect i.e., they continue to suppress the bacterial multiplication even after their plasma concentration falls below the MIC. Aminoglycosides and fluoroquinolones have such effect against gram-negative bacteria.

COMBINATION OF ANTIMICROBIALS

Use of a combination of antimicrobials may have synergistic, antagonistic or indifferent (no change) effects. Hence appropriate drugs should be used for combination.

Two bactericidal drugs given together (e.g: Penicillin + aminoglycosides) are generally synergistic.

Combination of a bacteriostatic with a bactericidal drug is not useful because bacteriostatic drugs inhibit the multiplication

Table 35.1: Choice of antibiotics recommended in the treatment of some common infections

Microorganisms	Diagnosis	Drug of first choice	Alternative drugs
<i>Gram-positive organisms</i>			
<i>Group A Streptococcus</i>	Pharyngitis, Otitis media, Sinusitis, Cellulitis, Erysipelas, Impetigo, Bacteraemia	Penicillin or amoxicillin	Erythromycin, A first generation cephalosporin
<i>Group B Streptococcus</i>	Bacteraemia Endocarditis Meningitis	Ampicillin or penicillin + an aminoglycoside	A first generation cephalosporin
<i>Staphylococcus aureus</i>	Furuncle, Cellulitis, Bacteraemia, Osteomyelitis, Pneumonia		
• Methicillin sensitive		Cloxacillin or dicloxacillin	A first generation cephalosporin or vancomycin
• Methicillin resistant		Vancomycin	Ciprofloxacin + rifampicin Quinupristine- dalbopristine, Linezolid
<i>Pneumococcus</i>	Pneumonia, Sinusitis, Otitis, Endocarditis Meningitis	Penicillin Amoxicillin	A first generation cephalosporin
<i>Penicillin resistant</i>	–	Ceftriaxone Cefotaxime Vancomycin	Clindamycin Cotrimoxazole
<i>Enterococcus</i>	Endocarditis	Penicillin G + gentamicin	Vancomycin + gentamicin
<i>Gonococcus</i>	Gonorrhoea, Pelvic inflammatory disease	Ceftriaxone	Ampicillin Amoxicillin Doxycycline Erythromycin
<i>Meningococcus</i>	Meningitis	Ceftriaxone Cefotaxime Rifampicin	Penicillin G Chloramphenicol Minocycline
<i>Corynebacterium diphtheriae</i>	Diphtheria	Erythromycin	A first generation cephalosporin Clindamycin
<i>Clostridium tetani</i>	Tetanus	Penicillin G Doxycycline	Clindamycin
<i>Clostridium difficile</i>	Pseudomembranous colitis	Metronidazole	Vancomycin
<i>Clostridium perfringens</i>	Gas gangrene	Penicillin G	Ceftizoxime Cefoxitin Chloramphenicol Doxycycline

Contd...

Contd...

Microorganisms	Diagnosis	Drug of first choice	Alternative drugs
<i>Bacillus anthracis</i>	Malignant pustule, pneumonia	Penicillin G	Erythromycin Doxycycline A first generation cephalosporin
<i>Gram-negative organisms</i>			
<i>Escherichia coli</i>	Urinary tract infection	Norfloxacin Ciprofloxacin Cotrimoxazole	Ampicillin + gentamicin; Amoxicillin + clavulanic acid; Aztreonam
<i>Proteus mirabilis</i>	Urinary tract infection Bacteraemia and other infections	Ampicillin or Amoxicillin	Cephalosporin - I or IIG Ciprofloxacin A cephalosporin Gentamicin
<i>Pseudomonas aeruginosa</i>	Urinary tract infection	A broad spectrum penicillin + Ciprofloxacin	Gentamicin Ceftazidime A cephalosporin Imipenem Aztreonam
<i>Klebsiella pneumoniae</i>	Urinary tract infection Pneumonia	A cephalosporin A cephalosporin + gentamicin	Mezlocillin/ Piperacillin An aminoglycoside Mezlocillin/ Piperacillin Aztreonam Amoxicillin + clavulanic acid
<i>Salmonella</i>	Typhoid fever Bacteraemia	Ciprofloxacin Ceftriaxone	Chloramphenicol Ampicillin Cotrimoxazole
<i>Shigella</i>	Gastroenteritis	Ciprofloxacin or norfloxacin	Cotrimoxazole Ampicillin
<i>Haemophilus influenzae</i>	Sinusitis Pneumonia Otitis media	Amoxicillin + clavulanic acid Cotrimoxazole	Amoxicillin Ciprofloxacin Azithromycin A cephalosporin
	Meningitis	Ceftriaxone	Chloramphenicol Ampicillin + sulbactam
<i>Haemophilus ducreyi</i>	Chancroid	Ceftriaxone Cotrimoxazole	Ciprofloxacin Erythromycin Doxycycline
<i>Brucella</i>	Brucellosis	Doxycycline + rifampicin	Cotrimoxazole Gentamicin
<i>Yersenia pestis</i>	Plague	A tetracycline + streptomycin	Doxycycline Chloramphenicol Ciprofloxacin

Contd...

Contd...

Microorganisms	Diagnosis	Drug of first choice	Alternative drugs
<i>Vibrio cholerae</i>	Cholera	Doxycycline Ciprofloxacin	Cotrimoxazole Chloramphenicol
<i>Campylobacter jejuni</i>	Enteritis	Ciprofloxacin	Erythromycin
<i>Treponema pallidum</i>	Syphilis	Penicillin G	Ceftriaxone Doxycycline
<i>Leptospira</i>	Weil's disease	Penicillin G	Doxycycline
<i>Helicobacter pylori</i>	Meningitis Peptic ulcer	Metronidazole + amoxicillin + Bismuth/omeprazole	Omeprazole+ amoxicillin+ clarithromycin
<i>Legionella</i>	Pneumonia	Azithromycin + rifampicin	Erythromycin Clarithromycin Doxycycline Ciprofloxacin + rifampicin
Other agents			
<i>Mycoplasma pneumoniae</i>	Atypical pneumonia	Erythromycin Doxycycline	Azithromycin
<i>Rickettsiae</i>	Typhus fever, Q fever Rocky mountain spotted fever	Doxycycline	Chloramphenicol
<i>Chlamydia trachomatis</i>	Lymphogranuloma venereum Trachoma Inclusion conjunctivitis Urethritis	Doxycycline	Erythromycin Azithromycin
<i>Chlamydia psittaci</i>	Psittacosis	Doxycycline	Chloramphenicol
<i>Chlamydia pneumoniae</i>	Pneumonia	Doxycycline	Erythromycin Azithromycin
<i>Pneumocystis jirovecii</i> and <i>P. carinii</i>	Pneumonia	Cotrimoxazole	Trimethoprim Atovaquone + proguanil Dapsone

of bacteria and thereby antagonize the effect of bactericidal drugs (as bactericidal drugs act on actively multiplying bacteria). Hence such combinations should be avoided.

A combination of antimicrobial agents is indicated in certain specific situations. The combination serves one of the following purposes.

1. *To obtain synergism* Combination of antibiotics to attain synergism is recommended in -

- *Bacterial endocarditis*–
Penicillin + streptomycin/gentamicin is synergistic.
- *Pseudomonas infections*–
Carbenicillin + gentamicin

- *Pneumocystis carinii pneumonia*–
Trimethoprim + sulfamethoxazole
 - β -lactamase producing organisms like
H. influenzae –
Amoxicillin + clavulanic acid
 - *Tuberculosis* – INH + rifampicin.
2. *Treatment of mixed infections* Oro-dental, intra-abdominal infections, brain abscesses, genitourinary infections and traumatic wound infections are often mixed infections. Aerobic and anaerobic organisms may be involved. Two or more antimicrobials can be used depending on the culture and sensitivity report. Dentists generally use a combination of a penicillin/cephalosporin/macrolide with metronidazole.
 3. *Initial treatment of severe infections* Drugs covering both gram-positive and gram-negative pathogens may be used initially till the culture report is available, e.g. penicillin + aminoglycoside; cephalosporin + aminoglycoside. If anaerobes are likely to be present, metronidazole may be added. Samples for culture should however be taken before starting the antibiotics.
 4. *To prevent the emergence of resistance* In the treatment of tuberculosis and leprosy, combination of drugs is used to prevent the development of resistance.
 5. *To reduce the adverse effects* The doses needed may be lower when a combination is used. This may reduce the incidence and severity of adverse effects, e.g. Amphotericin B + flucytosine in cryptococcal meningitis.

Disadvantages of Antimicrobial Combination

1. Risk of toxicity from each agent—especially if toxicity is overlapping—may get added up e.g. many antitubercular drugs are hepatotoxic. Toxicity of one drug may be enhanced by another e.g.,
Vancomycin + aminoglycoside → more severe renal toxicity
2. Selection of resistant strains—The few resistant mutants that remain may multiply unchecked.
3. Emergence of organisms resistant to multiple drugs.
4. Increased cost of therapy.

CHEMOPROPHYLAXIS

Chemoprophylaxis is the use of antimicrobial agents to prevent infection.

In dentistry— Prophylactic use of antibiotics may not be required in routine dental treatment if the patient's immune function is normal. Certain dental procedures, including deep scaling, tooth extraction, periodontal procedures, oral and maxillofacial surgeries can produce transient bacteremia. In patients at special risk including those with depressed immunity, insertion of prosthesis, implants and prolonged surgeries would require antibiotic prophylaxis (Table 35.2). In general chemoprophylaxis is recommended in the following situations:

1. *To protect healthy persons*
 - Penicillin G is given for prevention of gonorrhoea or syphilis in patients after contact with infected persons - postexposure prophylaxis.
 - For preventing meningococcal infection in healthy children during an epidemic—rifampicin or sulfonamides may be used.
 - Malaria- In healthy individuals visiting an endemic area.
2. *To prevent infection in high risk patients*
 - In neutropenic patients- like patients receiving anticancer drugs, immunosuppressive agents and patients with AIDS, a penicillin or fluoroquinolones or cotrimoxazole may reduce the incidence of bacterial infection.
 - In patients with valvular heart diseases prosthetic heart valves, and previous

Table 35.2: Antibiotics used in dentistry for chemoprophylaxis

Antibiotic	Dose*	Route
1. Cefazolin	1 g	IV
2. Clindamycin + gentamicin	600 mg 1.5 mg/kg	IV
3. Amoxicillin	2 g	Oral
4. Cephalexin	2 g	Oral
5. Erythromycin	1 g	Oral
For contaminated, traumatic, orofacial wounds		
6. Amoxicillin + Clavulanic acid	750 125 mg	Oral

* all single dose except no. 6.

history of bacterial endocarditis even minor procedures like dental extraction, tonsillectomy or endo-scopies may result in bacterial endocarditis (damage to mucosa results in bacteremia leading to endocarditis). Penicillin is used for prophylaxis.

- In patients with contaminated or exposed wounds as in road traffic accidents.
 - Catheterisation of urinary tract - norfloxacin is used.
 - In burns - to prevent colonisation by bacteria.
3. *Surgical prophylaxis* Certain guidelines are to be followed:
- Adequate antibacterial activity should be present during surgery. Hence the drug should be started 30-60 minutes before surgery.
 - The drug should not be continued beyond 24 hours after surgery (risk of resistance development).
 - The drug should be effective against all organisms that are likely to contaminate the wound.
 - A single dose of 1 gm IV cefazolin injection is the most commonly used. In patients allergic to it, clindamycin 600 mg IV+ gentamicin 1.5 mg/kg IV may be given.

4. *In close contacts-*

Chemoprophylaxis is recommended particularly in children when infectious (open) cases of leprosy (dapsone) or tuberculosis (INH, rifampicin) are in close contact.

SUPERINFECTION

Superinfection/suprainfection is the appearance of a new infection resulting from the use of antimicrobials. Antibacterials alter the normal microbial flora of the intestinal, respiratory and genitourinary tracts. The normal flora contribute to host defence mechanisms as follows—they inhibit colonisation of pathogenic organisms by producing antibacterial substances called bacteriocins and by competing for nutrients. When the normal flora are destroyed by antibacterials, there can be dangerous infections due to various organisms especially the normal commensals. The broader the antibacterial spectrum of a drug, the more are the chances of superinfection, as the alteration of the normal flora is greater (Table 35.3). *Sites involved*—intestinal, respiratory and genitourinary tracts.

MISUSE OF ANTIBIOTICS

Antibiotics are one of the most overused or misused drugs. Faulty practices like the use of antibacterials in viral infections which are

Table 35.3: Common microorganisms causing superinfection

<i>Microorganisms</i>	<i>Manifestations</i>	<i>Treatment</i>
<i>Candida albicans</i>	Oral thrush, diarrhoea, vaginitis	Clotrimazole
<i>Staphylococci</i>	Enteritis	Cloxacillin
<i>Clostridium difficile</i>	Pseudomembranous colitis	Metronidazole, Vancomycin
<i>E.coli</i>	UTI	Norfloxacin
<i>Pseudomonas aeruginosa</i>	UTI	Carbenicillin

self-limiting, using too low doses or unnecessarily prolonged treatment, using antibiotics in all fever cases—are all irrational and can do more harm than any benefit.

PROBIOTICS

Probiotics are products containing viable, non-pathogenic micro-organisms adminis-

tered orally to alter the intestinal microflora. *Lactobacillus*, *Bifido bacterium*, *Streptococcus salivarius*, some *enterococci* and *Saccharomyces boulardii* are some of the presently tried probiotics. Studies have shown them to be useful in acute infectious diarrhoea and antibiotic induced diarrhoea. Probiotics have also been tried in ulcerative colitis and irritable bowel syndrome.

36

Sulfonamides, Cotrimoxazole and Quinolones

SULFONAMIDES

Sulfonamides were the first effective antibacterial agents to be used systemically in man. They are synthetic agents that contain a sulfonamide group.

Antibacterial spectrum Sulfonamides inhibit gram-positive and some gram-negative bacteria, nocardia, chlamydiae, *Plasmodium falciparum* and *Toxoplasma gondii*.

Mechanism of Action

PABA

↓ *Folic acid synthetase* ← Sulfonamides
Dihydrofolic Acid

Bacteria synthesize their own folic acid from p-amino benzoic acid (PABA) with the help of the enzyme folic acid synthetase. Sulfonamides are structurally similar to PABA and competitively inhibit the enzyme folic acid synthetase. This results in folic acid deficiency and injury to the bacterial cell.

Human cells are not affected because they require preformed folic acid supplied from the diet and cannot synthesize folic acid by themselves. Sulfonamides are *bacteriostatic*.

Presence of pus, blood and tissue breakdown products make sulfonamides ineffective as these are rich in PABA.

Resistance Bacteria acquire resistance to sulfonamides by:

1. Mutations—resulting in over production of PABA.
2. Using alternative metabolic pathway for folic acid synthesis.
3. Low permeability to sulfonamides.

Classification

1. *Short-acting*
Sulfisoxazole, sulfadiazine
2. *Intermediate-acting*
Sulfamethoxazole
3. *Long-acting*
Sulfamethoxypyridazine,
Sulfadoxine
4. *Poorly absorbed*
Sulfasalazine
5. *Topical*
Sulfacetamide, mafenide
Silver sulfadiazine.

Pharmacokinetics Sulfonamides are well-absorbed, extensively bound to plasma proteins and are well distributed to all tissues. They are metabolized in the liver by acetylation.

Adverse Effects

1. Renal irritation, haematuria, albuminuria and crystalluria—due to precipitation of the

drug in acidic urine. This can be avoided by intake of large volumes of fluids and by alkalinising the urine.

2. Hypersensitivity reactions like rashes, fever, Stevens Johnsons syndrome and rarely exfoliative dermatitis.
3. Anorexia, nausea and abdominal pain.
4. Haemolytic anaemia in patients with G₆PD deficiency.
5. Kernicterus–sulfonamides displace bilirubin from the binding sites which crosses the BBB and may cause kernicterus in the newborn. Hence sulfonamides are contraindicated in pregnancy and in infants.

Uses

Because of the development of resistance and availability of better antimicrobials, sulfonamides are not commonly used now except in a few cases.

1. *Urinary tract infections* Sulfonamides may be used in areas where resistance is not high.
2. *Nocardiosis* High doses of sulfonamides can be used.
3. *Toxoplasmosis* Sulfonamides with pyrimethamine is the treatment of choice.
4. *Trachoma and inclusion conjunctivitis* Tetracyclines are the drugs of choice; sulfonamides are used as alternatives.
5. *Lymphogranuloma venereum and chancroid* Sulfonamides are used as alternatives to tetracyclines.
6. *Malaria* Sulfadoxine is used with pyrimethamine in chloroquine resistant malaria.
7. *Prophylactic use* In patients allergic to penicillins, sulfonamides may be used for prophylaxis of streptococcal pharyngitis in rheumatic fever.
8. *Topical* Sulfacetamide eye drops are used in bacterial conjunctivitis; mafenide and silver sulfadiazine are used in burns to prevent infection.
9. *Ulcerative colitis* Sulfasalazine is useful in ulcerative colitis and rheumatoid arthritis.

COTRIMOXAZOLE

The combination of trimethoprim and sulfamethoxazole is cotrimoxazole. Trimethoprim is effective against several gram-positive and gram-negative organisms. But when used as a sole agent, resistance develops rapidly.

Mechanism of action Sulfonamides inhibit the conversion of PABA to dihydrofolic acid (DHF) (Fig. 36.1) and trimethoprim inhibits dihydrofolate reductase (DHFR) and thus prevents the reduction of DHF to tetrahydrofolic acid (THF). The two drugs thus block sequential steps in folic acid synthesis and the combination is bactericidal.

The ratio of 'trimethoprim : sulfamethoxazole' used is 1:5 to attain the right plasma concentration. Among sulfonamides, sulfamethoxazole is chosen because its pharmacokinetic properties closely match with that of trimethoprim.

Antibacterial spectrum Cotrimoxazole is effective against several gram-positive and gram-negative organisms like *Staph. aureus*, *streptococci*, *meningococci*, *C. diphtheriae*, *E. coli*, *Proteus*, *H. influenzae*, *Salmonella* and *Shigella*.

Resistance Development of resistance to the combination is slower when compared to either drugs given alone. Bacteria may acquire resistance by mutation or by acquisition of a plasmid coding for an altered DHFR.

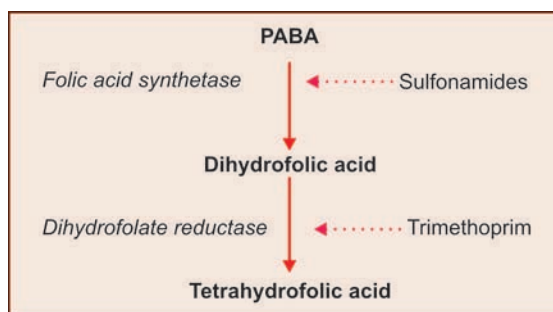


Fig. 36.1: Sequential blockade in folic acid synthesis

Adverse Effects

- Nausea, vomiting, headache, glossitis, stomatitis and allergic skin rashes are relatively common. In fact all the adverse effects to sulphonamides can also be seen with cotrimoxazole because it contains sulfamethoxazole.
- In patients with folate deficiency, cotrimoxazole may precipitate megaloblastic anaemia.
- Haematological reactions like anaemia and granulocytopenia are rare.
- AIDS patients are more prone to adverse effects to cotrimoxazole.
- Patients with renal disease may develop uraemia.

Preparations

Trimethoprim Sulfamethoxazole (SEPTRAN, CIPLIN)

80 mg	400 mg
160 mg	800 mg–double strength (DS)

Uses

1. *Urinary tract infection* Uncomplicated acute UTI is treated for 7-10 days (DS, twice a day) with cotrimoxazole. Chronic and recurrent UTI–small doses are given for prophylaxis. Bacterial prostatitis–Trimethoprim attains high concentration in prostatic fluid.
2. *Respiratory tract infections* Upper and lower respiratory infections including bronchitis, sinusitis and otitis media respond.
3. *Bacterial gastroenteritis* due to *Shigella* and *E. coli* respond to cotrimoxazole.
4. *Typhoid* Cotrimoxazole is used as an alternative to fluoroquinolones.
5. *Pneumocystis carinii infection* (now identified as *Pneumocystis jiroveci*) Cotrimoxazole is used for prophylaxis and high doses for treatment of *Pneumocystis carinii* pneumonia in neutropenic and

AIDS patients. It also protects against infection with other gram-negative bacteria.

6. *Chancroid* Cotrimoxazole (DS, BD for 7 days) is the drug of choice.
7. *Oro-dental infections*–Cotrimoxazole may be used the treatment of mild infections as an alternative to penicillin.

QUINOLONES

The quinolones are a group of synthetic antimicrobial agents. Nalidixic acid is the older agent in the group. Oxalinic acid and cinoxacin are other quinolones.

Nalidixic Acid

Nalidixic acid is bactericidal against various gram-negative organisms like *E. coli*, *Shigella*, *Proteus* and *Klebsiella*. Its mechanism of action is same as that of fluoroquinolones (see below). Nalidixic acid is well absorbed orally. However, the plasma concentration of the drug is inadequate to have systemic effects but it attains high concentrations in the urine.

Adverse effects Haemolytic anaemia, allergic reactions and CNS effects like headache, myalgia and drowsiness may be encountered.

Uses

Nalidixic acid is used in uncomplicated UTI and diarrhoea due to *E.coli*, *Shigella* and *Proteus* (GRAMONEG 0.5-1g 3-4 times a day). *Oxalinic acid* and *cinoxacin* have properties and uses similar to nalidixic acid.

FLUOROQUINOLONES

The quinolones were fluorinated to obtain compounds with a wider spectrum of activity, fewer side effects, lesser chance of resistance and better tissue penetration when compared to quinolones. The fluoroquinolones (FQs) include *norfloxacin*, *ciprofloxacin*, *pefloxacin*,

ofloxacin, lomefloxacin and sparfloxacin—many more are being added. The newer agents include *trovafloxacin, gatifloxacin, moxifloxacin*, and *clinafloxacin*.

Mechanism of Action

Fluoroquinolones are bactericidal. They inhibit the bacterial enzyme DNA gyrase (topoisomerase II) which is required for DNA replication and transcription.

During DNA replication there is positive supercoiling of the DNA. This is corrected by the enzyme DNA gyrase by introducing negative supercoils and therefore this enzyme is necessary for DNA replication. By inhibiting the enzyme DNA gyrase, fluoroquinolones inhibit DNA replication.

Resistance is comparatively not very frequent due to the unique mechanism of action. Resistance is due to mutations in the target enzyme or a change in the permeability of the organism. Several strains of *E.coli*, *Staphylococci*, *Pseudomonas* and *Serratia* have now developed resistance.

Antibacterial spectrum Gram-negative organisms like gonococci, meningococci, *H. influenzae*, *E. coli*, *Salmonella*, *Shigella*, enterobacteria; *H. pylori* and gram-positive organisms like staphylococci; chlamydiae, mycoplasma and mycobacterium are susceptible. Some of the newer fluoroquinolones are effective against some anaerobic organisms and *Streptococcus pneumoniae*.

Pharmacokinetics On oral administration, fluoroquinolones are well-absorbed and widely distributed. Food and antacids interfere with absorption; Pefloxacin and ofloxacin cross the BBB. All FQs are metabolised by hepatic microsomal enzymes and FQs are microsomal enzyme inhibitors – can result in related drug interactions. These drugs are excreted by the kidneys. Hence dose should be reduced in renal failure. Plasma $t_{1/2}$ varies from 3 hrs (norfloxacin), 10 hrs (pefloxacin) to 18-20 hrs (sparfloxacin given once daily) (Table 36.1).

Adverse reactions Fluoroquinolones are well-tolerated. Nausea, vomiting, abdominal discomfort, diarrhoea and rashes may be seen. Tendinitis with associated risk of tendon rupture has been reported. Fluoroquinolones damage the growing cartilage resulting in arthropathy and are therefore contraindicated upto 18 years of age. CNS effects include headache and dizziness. In patients receiving NSAIDs and other epileptogenic drugs like theophylline, fluoroquinolones can sometimes precipitate seizures. Grepafloxacin was found to cause cardiac arrhythmias due to which it has already been withdrawn from the market.

Uses

1. **Urinary tract infections** Very effective in UTI even when caused by multi-drug resistant bacteria—norfloxacin is generally used (400 mg—BD for 5-10 days).
2. **Typhoid** Ciprofloxacin is the drug of choice (500 mg BD—10 days)— it also eradicates carrier state.
3. **Diarrhoea** due to *Shigella*, *E.coli* and *Campylobacter* respond.
4. **Gonorrhoea** Single dose 250 mg ciprofloxacin is curative. Ciprofloxacin is used for 3 days.
5. **Chancroid** As an alternative to cotrimoxazole-ciprofloxacin is used for 3

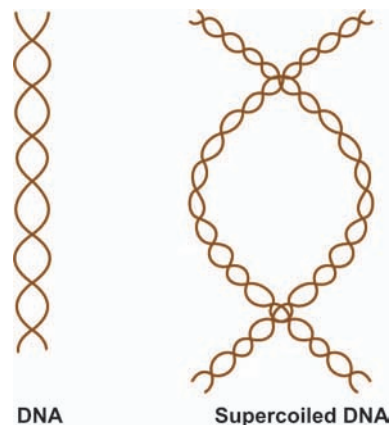


Fig. 36.2: Schematic diagram of DNA

- days. Chlamydial urethritis, cervicitis, ciprofloxacin or sparfloxacin can be used as alternatives to tetracyclines.
6. *Respiratory tract infections*—due to *H. influenzae*, *Legionella* and *Mycoplasma* can be treated with fluoroquinolones.
 7. *Bone, joint, soft tissue and intra abdominal infections* — osteomyelitis and joint infections require prolonged treatment. Soft tissue infections due to sensitive bacteria can be treated with fluor-quinolones.
 8. *Tuberculosis* Ciprofloxacin is one of the drugs in multi-drug regimens used for resistant tuberculosis. It is also useful in atypical mycobacterial infections.
 9. Bacterial prostatitis and cervicitis-FQs are useful.
 10. Eye infections-Ciprofloxacin and ofloxacin may be used topically in the treatment of eye infections.
 11. Anthrax - also responds to fluoro-quinolones.
 12. Oro dental infections—Levofloxacin, ofloxacin, gatifloxacin and moxifloxacin are all long acting, orally effective and have moderate efficacy against some anaerobes. They can be used in the prevention and treatment of orodental infections.

Table 36.1: Dose and route of administration of some fluoroquinolones

Drug	Dose and route	Remarks
Norfloxacin (NORFLOX)	Oral: 400 mg BD	Preferred in urinary and genital infections
Ciprofloxacin (CIPLOX)	Oral: 250-750 mg BD IV: 100-200 mg 12 h	Most widely used fluoroquinolone
Pefloxacin (PEFLOX)	Oral: 400 mg BD IV: 400 mg q 12 h	Penetration into CSF is good
Ofloxacin (TARIVID)	Oral: 200-400 mg OD IV: 200-400 mg q 12-24 h	Indicated in urinary and respiratory tract infections and gonorrhoea; Effective in chlamydial infections
Levofloxacin	Oral: 500 mg OD	Better activity against gram-positive organisms and atypical pneumonia pathogens; excreted mainly through kidneys
Lomefloxacin (LOMEF)	Oral: 400 mg OD	Has a long $t_{1/2}$
Sparfloxacin (SPARLOX)	Oral: 200-400 mg OD	Enhanced activity against gram positive organisms and in atypical pneumonia; also useful in chlamydial infections.
Gatifloxacin	Oral : 400 mg OD	Better activity against gram positive organisms and atypical pneumonia pathogens.
Trovafoxacin Moxifloxacin some	Oral : 200 mg Oral : 400 mg OD	Excreted by non-renal mechanisms. High activity against gram positive bacteria and anaerobes. To be avoided in patients with risk of seizures.

Beta-lactam Antibiotics

The β -lactam antibiotics have a β -lactam ring. Penicillins, cephalosporins, monobactams and carbapenems are β -lactam antibiotics.

PENICILLINS

Sir Alexander Fleming discovered penicillin in 1928. Penicillins are one of the most important groups of antibiotics. Penicillin is now obtained from the fungus *Penicillium chrysogenum*.

Mechanism of Action

The β -lactam antibiotics act by inhibiting the cell wall synthesis in the bacteria.

The rigid cell wall of the bacteria protects it from lysis. Peptidoglycan—a complex polymer, is an important component of the cell wall. It consists of glycan chains which are cross-linked by peptide chains. The synthesis of this peptidoglycan requires enzymes called transpeptidases. β -lactam antibiotics inhibit these transpeptidases and thus inhibit the synthesis of the peptidoglycan, resulting in the formation of cell wall deficient bacteria. Such bacteria undergo lysis. Thus penicillins are bactericidal.

Classification

- A. Natural— Penicillin G
- B. Semisynthetic
 - 1. *Acid resistant*—Penicillin V
 - 2. *Penicillinase resistant*—
 - Methicillin, Oxacillin, Cloxacillin, Nafcillin
 - 3. *Aminopenicillins*—
 - Ampicillin, Bacampicillin, Amoxicillin
 - 4. Antipseudomonal penicillins
 - *Carboxypenicillins*—
 - Carbenicillin, Ticarcillin
 - *Ureidopenicillins*—
 - Azlocillin, Mezlocillin, Piperacillin.

NATURAL PENICILLINS

Penicillin G (Benzyl Penicillin)

Antibacterial spectrum Penicillin G (PnG) has a narrow antibacterial spectrum (Table 37.2) and is effective against gram-positive cocci and bacilli and a few gram-negative cocci. Thus streptococci, pneumococci, gonococci, meningococci, *B. anthracis*, *C. diphtheriae*, clostridia, listeria and spirochetes are highly sensitive.

Resistance Many organisms like staphylococci produce a penicillinase which is a beta-

lactamase—which opens the β -lactam ring and inactivates penicillins. Altered target proteins on the bacterial cell which reduces affinity for penicillins also lead to resistance. *Pharmacokinetics* PnG is destroyed by gastric juice; food interferes with its absorption — hence it is to be given 2 hr after food. It has a short $t_{1/2}$ of 30 min. Though it does not readily cross the BBB, in presence of inflammation of the meninges, therapeutic concentration is attained in the CSF. It is excreted by the kidneys. Probenecid blocks the renal tubular secretion of penicillin and thereby prolongs its duration of action.

Preparations and dose PnG is mainly given parenterally though orally effective form—

potassium PnG is also available. Oral penicillin is used only in minor infections. Since benzyl penicillin is short-acting, repository forms like procaine penicillin and benzathine penicillin, which are longer-acting are made available. Given deep IM they release penicillin slowly from the site. Procaine penicillin is given 12-24 hourly while a single injection of benzathine penicillin is effective for 3-4 weeks. For preparation and dose see Table 37.1.

Adverse Effects

Hypersensitivity PnG is the most common cause of drug allergy. Manifestations range

Table 37.1: Preparations, dose and route of administration of penicillins

Drug	Dose	Route	Trade name
NATURAL PENICILLINS			
Sodium penicillin G (Crystalline penicillin)	0.5-5 MU q 4-6 hr	IM/IV	CRYSTAPEN
Procaine penicillin G	0.5-1 MU q 12-24 hr	IM	PROCAINE PENICILLIN G
Benzathine penicillin G	1.2-2.4 MU every 3-4 weeks	Deep IM	PENIDURE LA
SEMISYNTHETIC PENICILLINS			
Penicillin V	250-500 mg QID	Oral	CRYSTAPEN-V
Cloxacillin	250-500 mg QID	Oral	KLOX
Dicloxacillin	250-500 mg QID	Oral	BIOCLOX
Nafcillin	1-2 gm q 4-6 hr	IV	UNIPEN
Ampicillin	250 mg to 1 gm QID	Oral IM/IV	AMPICILLIN ROSCILLIN
Ampicillin + sulbactam	1 gm Ampi + 0.5 gm sulb q 6-8 hr	IV	SULBACIN
Amoxicillin	250-500 mg TID	Oral	NOVAMOX SYNAMOX
Amoxicillin + clavulanic acid	250 mg Amox + 125 mg Clav TID	Oral	AUGMENTIN
Piperacillin	3-4 gm q 4-6 hr	IV	PIPRAPEN
Piperacillin+tazobactam	4g Pip+0.5g tazo q 8 hr	IV	ZOSYN
Ticarcillin	3 gm q 4-6 hr	IV	TICAR
q4-6hr — every 4 to 6 hours.	MU-Mega Unit		

from skin rashes, urticaria, fever, bronchospasm, serum sickness and rarely exfoliative dermatitis and anaphylaxis. Though all forms of penicillins can cause allergy, anaphylaxis is more common following parenteral than oral preparations. The highest incidence is with procaine penicillin where allergy is most often due to the procaine component. There is cross-sensitivity among different penicillins. Topical penicillins are highly sensitizing and their use is banned.

History of allergy to penicillins should be taken before prescribing; incidence of allergy is higher among atopic individuals. A scratch test or intradermal sensitivity test with 2-10 units should be done. Even if this is negative, it does not completely rule out allergy. Penicillin should be given cautiously and a syringe loaded with adrenaline to treat anaphylaxis should be kept ready.

Other Adverse Effects

Local Pain at the site of injection, thrombophlebitis on IV injection.

CNS Large doses of PnG may produce confusion, muscle twitchings, convulsions and coma.

Suprainfections are rare due to its narrow spectrum of activity.

Jarisch-Herxheimer reaction When penicillin is injected in a patient with syphilis, there is sudden destruction of spirochetes and release of its lytic products. This triggers a reaction with fever, myalgia, shivering, exacerbation of syphilitic lesions and vascular collapse.

Uses

Penicillin G is the antibiotic of choice for several infections unless the patient is allergic to it.

(A) Orodental infections—Penicillin G is effective against a variety of aerobic and

anaerobic microorganisms and therefore very useful in most orodental infections. However the disadvantages of parenteral administration and hypersensitivity reactions have limited its use. Procaine Penicillin can be used IM.

(B) Other infections

1. **Pneumococcal infections** For infections like pneumonia, meningitis and osteomyelitis due to penicillin-sensitive pneumococci, PnG is the *drug of choice*.
2. **Streptococcal infections** Pharyngitis, sinusitis, pneumonia, meningitis and endocarditis are all treated with penicillin. Infective endocarditis due to *Strep. viridans* is treated with high dose PnG ± an aminoglycoside.
3. **Meningococcal infections** PnG is the drug of choice for all meningococcal infections.
4. **Staphylococcal infections** Since most staphylococci produce penicillinase, a penicillinase resistant penicillin should be used.
5. **Syphilis** is treated with procaine penicillin for 10 days or with benzathine penicillin.
6. **Diphtheria** Antitoxin is the only effective treatment. PnG eliminates carrier state - PP₆ given for 10-12 days.
7. **Anaerobic infections** Pulmonary, periodontal and brain abscesses due to anaerobes respond to PnG.
8. **Actinomycosis** PnG is the drug of choice for all forms of actinomycosis. 12 to 20 MU should be given for 6 weeks.
9. **Tetanus and gas gangrene** Antitoxin is the treatment for tetanus—but PnG has adjuvant value.
Gas gangrene— PnG is the *drug of choice*.
10. **Other infections** PnG is the *agent of choice* for infections like anthrax, trench mouth, rat bite fever and listeria infections.
11. **Prophylactic uses:**
 - **Rheumatic fever** Benzathine penicillin 1.2 MU every month prevents colonisation by streptococci and thereby decreases

the recurrences of rheumatic fever. It is to be continued for several years.

- *Gonorrhoea and syphilis* Sexual contacts are effectively protected against these diseases when treated with penicillin within 12 hours of exposure.
- *Valvular heart diseases*—25% cases of bacterial endocarditis are seen following dental extractions. Patients with valvular heart diseases undergoing dental extractions, endoscopies and other minor surgical procedures that may cause bacteraemia should be given penicillin prophylaxis.

Disadvantages of natural penicillins are:

1. they are not effective orally.
2. have a narrow spectrum of activity.
3. are susceptible to β lactamase.
4. can cause hypersensitivity.

To overcome the above disadvantages, semisynthetic penicillins have been introduced.

SEMISYNTHETIC PENICILLINS

Acid resistant penicillins **Penicillin V** (Phenoxymethyl penicillin) is acid stable and can be given orally. It is used only in mild streptococcal pharyngitis, sinusitis and trench mouth.

Dose 250-500 mg 6 hourly.

Penicillinase resistant penicillins are resistant to hydrolysis by penicillinase produced by bacteria. However, against other micro-organisms—they are less effective than PnG. *Methicillin* is destroyed by gastric juice—hence given parenterally. *Cloxacillin* is given orally. *Nafcillin* is highly resistant to penicillinase and also has useful activity against nonpenicillinase producing organisms. It requires parenteral administration because of its unreliable absorption from the gut.

Uses

Penicillinase resistant penicillins are the drugs of choice for infections with penicillinase producing staphylococci. Methicillin resistant strains have now emerged and are treated with vancomycin.

Extended Spectrum Penicillins

Aminopenicillins These agents cover a wider antibacterial spectrum including many gram-negative bacilli. They are orally effective but are sensitive to betalactamases.

Antibacterial spectrum Both gram-positive and gram-negative organisms including streptococci, meningococci, pneumococci, *H. influenzae*, *E. coli*, *Proteus*, *Salmonella*, *Shigella* and *Klebsiella* are sensitive. Many strains are now resistant.

Ampicillin is well-absorbed orally; food interferes with absorption. It is excreted mainly through kidneys.

Adverse effects Diarrhoea due to irritation of the gut by the unabsorbed drug is the most common adverse effect with ampicillin. Skin rashes are also fairly frequent.

Uses

1. *Respiratory tract infections* like bronchitis, sinusitis and otitis media respond to ampicillin.
2. *Urinary tract infections* Though ampicillin was the drug of choice earlier, many organisms have now become resistant.
3. *Meningitis* Ampicillin is given with a cephalosporin.
4. *Typhoid* Ampicillin is an alternative to ciprofloxacin.
5. *Septicaemia due to gram-negative organisms*. Intravenous ampicillin may be used, with an aminoglycoside.
6. *Dental infections*—Ampicillin is useful in the treatment of most orodental infections. However, diarrhoea has limited its use.

Bacampicillin is an ester of ampicillin. It is a prodrug that is better absorbed (hence diarrhoea is less common) and longer-acting than ampicillin.

Amoxicillin differs from ampicillin in the following:

1. Amoxicillin is better absorbed orally
2. Food does not interfere with its absorption
3. Diarrhoea is rare (because it is well absorbed).
4. Given thrice daily (Table 37.2).

Amoxicillin is used in similar infections as ampicillin like respiratory infections, prevention and treatment of infections in dental practice, *Salmonella* gastroenteritis and urinary tract infections. Amoxicillin is a component of the various regimens to eradicate *H. pylori*. Amoxicillin is preferred over ampicillin because of its advantages mentioned above.

ANTIPSEUDOMONAL PENICILLINS

Carboxypenicillins

Carbenicillin is effective in *Pseudomonas aeruginosa* and *Proteus* infections. Carbenicillin

is given parenterally while carbenicillin indanyl is effective orally. *Ticarcillin* has better activity against *P. aeruginosa*. All three are susceptible to penicillinase.

Adverse effects Carbenicillin is used as a sodium salt and in higher doses this excess sodium may cause oedema and CCF; may also cause bleeding due to abnormal platelet aggregation.

Ureidopenicillins

Ureidopenicillins have a wider antibacterial spectrum and are effective against *Pseudomonas* and *Klebsiella* infections. Moreover, their sodium content is low. Hence they have almost replaced carboxypenicillins. *Azlocillin*, *mezlocillin* and *piperacillin* are all administered intravenously. When combined with a beta lactamase inhibitor, piperacillin can be considered to have the broadest antibacterial spectrum among the penicillins.

Beta-Lactamase Inhibitors

β -lactamases are enzymes produced by bacteria that open up the β -lactam ring and

Table 37.2: Compare and contrast penicillin G and amoxicillin

Feature	Penicillin G	Amoxicillin
Source	Natural (<i>Penicillium chrysogenum</i>)	Semisynthetic
Acid stability	Acid labile	Acid stable
Antibacterial spectrum	Narrow (Mostly Gm+ve)	Wide (Gm+ve and Gm -ve)*
Route of administration	Parenteral only	Oral and parenteral
Duration of action	Short	Longer
Plasma $t_{1/2}$	30 minutes	2 hrs
Frequency of administration	QID	TID
Prominent adverse effect	Allergy	Diarrhoea
Structure	Has β lactam ring	Has β lactam ring
Penicillinase susceptibility	Yes	Yes
* Gm +ve - Gram positive		Gm -ve - Gram negative

inactivate the β -lactam antibiotics. β -lactamase inhibitors bind to and inactivate β -lactamases preventing the destruction of the β -lactam antibiotics. The antibacterial spectrum depends on the penicillin used. β -lactamase inhibitors are clavulanic acid, sulbactam and tazobactam.

Clavulanic acid inhibits β -lactamases and is combined with amoxicillin for both oral and parenteral administration. It extends the antibacterial spectrum of amoxicillin and the combination inhibits organisms like *betalactamase* producing *staphylococci*, *gonococci*, *E.coli* and *H. influenzae*. The combination is used for mixed aerobic-anaerobic infections including orodental infections, gonorrhoea and nosocomial infections. Clavulanic acid is also combined with ticarcillin.

Sulbactam is combined with ampicillin. It is given parenterally for mixed aerobic-anaerobic infections including orodental, intra-abdominal, gynaecological, surgical, pelvic and other infections.

Tazobactam is combined with piperacillin for parenteral administration.

They are available in fixed combinations.

Drugs	Route
Clavulanic acid + amoxicillin	Oral
Clavulanic acid + ticarcillin	IV
Sulbactam + ampicillin	IV
Tazobactam + piperacillin	IV

CEPHALOSPORINS

Cephalosporins are semisynthetic antibiotics with a beta-lactam ring related to penicillins. They are derived from cephalosporin-C and have a wider spectrum of activity than penicillins.

Mechanism of action Cephalosporins inhibit the bacterial cell wall synthesis similar to penicillins (see page 270).

Resistance As in the case of penicillins, beta-lactamases and altered target proteins determine resistance to cephalosporins.

Cephalosporins are classified into 4 generations as follows:

CLASSIFICATION

	Parenteral	Oral
First generation	Cephalothin Cefazolin	Cephalexin Cefadroxil
Second generation	Cefamandole Cefuroxime Cefotetan, Cefoxitin	Cefachlor Cefuroxime axetil
Third generation	Cefotaxime Ceftriaxone Cefoperazone Ceftizoxime Ceftazidime	Cefixime Cefpodoxime proxetil Cefdinir Ceftibuten
Fourth generation	Cefepime Cefpirome	

First Generation Cephalosporins

First generation cephalosporins are very effective against gram-positive organisms. Cephalothin is resistant to penicillinase, hence can be used in staphylococcal infections. Cefazolin has a longer $t_{1/2}$ and its tissue penetrability is good—Therefore used for surgical prophylaxis. Streptococci, staphylococci, *E.coli* and *Klebsiella* are inhibited. Cephalexin is used orally for minor infections like abscesses or cellulitis.

For preparations, dose and routes see Table 37.3.

Second Generation Cephalosporins

Second generation cephalosporins are more active against some gram-negative organisms compared to first generation ones. *H.*

Table 37.3: Preparations, doses and routes of administration of some cephalosporins

Drugs	Doses	Routes
Cephalothin (KAFLIN)	1-2 gm q 6 h	IV
Cefazolin (ALCIZON)	0.5-1 gm q 6 h	IM/IV
Cephalexin (SPORIDEX)	0.25-1 gm qid	Oral
Cefadroxil (DROXYL)	0.5-1 gm bid	Oral
Cefamandole (KEFADOL)	0.5-2 gm q 4-8 h	IM/IV
Cefuroxime (SUPACEF)	0.75-1.5 gm q 8 h	IM/IV
Cefuroxime axetil (CEFTUM)	0.25 -0.5 gm bid	Oral
Cefachlor (KEFLOR)	0.25-0.5 gm q 8 h	Oral
Cefotaxime (OMNATAX)	1-2 gm q 8 h	IM/IV
Ceftriaxone (OFRAMAX)	1-2 gm q 12-24 h	IM/IV
Cefoperazone (CEFOBID)	1-2 gm q 8-12 h	IM/IV
Cefixime (CEFSPAN)	0.2-0.4 gm q 12 h	Oral
Cefpodoxime proxetil (CEPODEM)	200-400 mg q 12 h	Oral
Cefpirome (CEFROM)	1-2 gm q 12 h	IV

influenzae, *E. coli*, *Proteus* and *Klebsiella* are inhibited. Cefuroxime is resistant to β -lactamases; attains good CSF concentration and is useful in meningitis. Cefoxitin and cefotitan are effective against *B. fragilis* and are used in mixed infections like in intraabdominal infections.

Third Generation Cephalosporins

Third generation cephalosporins are highly resistant to β -lactamases; have good activity against gram-negative organisms including *Citrobacter*, *Serratia*, *Enterobacteriaceae*, *Pseudomonas aeruginosa*, *N.gonorrhoeae* and *betalactamase* producing *H.influenzae*; but these have weak activity against gram positive cocci. Many cross BBB and are useful in meningitis. Ceftriaxone has a long $t_{1/2}$ and can be given once daily. It is excreted mainly through biliary tract and no dosage adjustment is needed in renal insufficiency. Ceftazidime is effective against *P.aeruginosa*.

Fourth Generation Cephalosporins

Fourth generation cephalosporins - cefepime and cefpirome are active against a variety of gram positive and gram negative organisms including streptococci, staphylococci, meningococci, gonococci, some enterococci, enterobacteriaceae, *H.influenzae* and *Pseudomonas aeruginosa*. They are more resistant to β lactamases. Both cefepime and cefpirome are administered parenterally. Cefepime attains good CSF levels while cefpirome has good tissue penetrability. Both are excreted almost completely through the kidneys.

The fourth generation agents are used in septicemia, nosocomial and other serious infections of the skin, respiratory and urinary tract as well as infections in immunocompromised patients.

Adverse Reactions

Cephalosporins are generally well-tolerated.

1. *Hypersensitivity reactions* like skin rashes, fever, serum sickness and rarely anaphylaxis are seen. 20% of patients allergic to penicillin show cross-reactivity to cephalosporins. There are no reliable skin tests for testing allergy.
2. *Nephrotoxicity* Mild nephrotoxicity is noted with some cephalosporins. Combination with other nephrotoxic drugs should be avoided.
3. *Diarrhoea* can result from some of the cephalosporins.
4. *Bleeding* is due to hypoprothrombinaemia which is more common in malnourished patients.
5. *Low WBC count* may be seen though rarely.
6. *Pain* at the injection site may occur.
7. *Disulfiram-like reaction* with alcohol is reported with some cephalosporins.
8. *Oro-dental infections*—Orally effective cephalosporins like cephalexin, cefaclor, cefuroxime axetil are used for the treatment of oro-dental infections. The latter two also have good activity against anaerobes which make them the preferred cephalosporins in dentistry. Cefazolin and cefotaxime are used for surgical prophylaxis in dental surgeries.

CARBAPENEMS

Carbapenems contain a β -lactam ring fused with a five-membered penem ring. Carbapenems include *imipenem*, *meropenem* and *ertapenem*.

Antibacterial spectrum – Carbapenems have a wide antibacterial spectrum and inhibit various gram-positive, gram-negative organisms and anaerobes including *streptococci*, *staphylococci*, *enterococci*, *Listeria*, *enterobacteriaceae*, *Pseudomonas* and *B. fragilis*.

Uses of Cephalosporins

1. *Gram-negative infections* Urinary, respiratory and soft tissue infections due to gram-negative organisms respond—a third generation agent is used.
2. *Surgical prophylaxis* Cefazolin is preferred due to its longer $t^{1/2}$ and better tissue penetrability for surgical prophylaxis including dental surgeries.
3. *Gonorrhoea* Ceftriaxone (single dose 250 mg) is the drug of choice.
4. *Meningitis* due to *H. influenzae*, *N. meningitidis* and *S. pneumoniae*—third generation agents are useful - cefotaxime or ceftriaxone may be used. *Pseudomonas meningitis* - ceftazidime + an aminoglycoside → very effective.
5. *Mixed aerobic-anaerobic infections*—common following pelvic surgeries—a third generation agent is used.
6. *Typhoid*—As an alternative to ciprofloxacin.
7. *Nosocomial infections* can be treated with third generation cephalosporins.

Mechanism of Action

Carbapenems inhibit bacterial cell wall synthesis similar to penicillins (see page 270). *Imipenem*—is not absorbed orally and is administered intravenously (250-500 mg every 6-8 hours); it has good tissue penetrability. Imipenem is inactivated quickly by a dehydropeptidase in the renal tubules. Hence it is always combined with cilastatin, an inhibitor of dehydropeptidase in order to prolong its plasma half life.

Adverse effects to imipenem include nausea, vomiting, diarrhoea and allergic reactions especially in patients allergic to other β -lactam antibiotics. High doses can occasionally cause seizures.

Uses

Imipenem-cilastatin is used in UTI, respiratory, skin, bone, soft tissue, intra-

abdominal and gynaecological infections due to susceptible microorganisms. It is particularly useful in enterobacter, penicillin-resistant pneumococci and other nosocomial infections resistant to other antibiotics. It is used with an aminoglycoside in pseudomonas infections.

Meropenem has the following advantages over imipenem-

- It is not destroyed by renal dipeptidase and therefore does not require to be combined with cilastatin.
 - Risk of seizures less than with imipenem.
- Indications of meropenem are similar to imipenem.

Ertapenem is similar to meropenem except that it is not useful against *P. aeruginosa*.

MONOBACTAMS

Monobactams are monocyclic beta-lactams, i.e they contain a single ring—the beta-lactam ring.

Aztreonam is the monobactam available. It is active against gram - negative bacilli including *Pseudomonas aeruginosa* but is not effective against gram-positive organisms and anaerobes. Aztreonam acts by inhibiting cell wall synthesis like penicillins. It is given parenterally (IM/IV 1-2 G every 6-8 hrs).

Aztreonam can be used in patients allergic to penicillins because there is no cross allergenicity with other β -lactams. The only reported adverse effects are occasional skin rashes. Aztreonam is used in pseudomonas infections especially nosocomial and in other gram-negative infections.

Broad Spectrum Antibiotics

TETRACYCLINES

Tetracyclines are antibiotics with four cyclic rings (hence the name) obtained from the soil actinomycetes. In addition to gram-positive and gram-negative bacteria, tetracyclines also inhibit the growth of other microorganisms like *Rickettsiae*, *Chlamydiae*, *Mycoplasma* and some protozoa. Therefore they are called *broad spectrum antibiotics*.

The tetracyclines include-

Tetracyclines	Semisynthetic derivatives
Chlortetracycline	Demeclocycline
Tetracycline	Methacycline
Oxytetracycline	Doxycycline
	Minocycline

Mechanism of action Tetracyclines are taken up by the susceptible microorganisms by active transport. The bacterial ribosome (Fig. 38.1) consists of 50S and 30S subunits. The tRNA carries amino acids to the ribosome for protein synthesis. The ribosome has three binding sites viz. A, P and E sites. Tetracyclines bind to 'A' site and prevent the binding of tRNA to this site. Thus they prevent protein synthesis and are *bacteriostatic*.

Antibacterial spectrum is broad including gram-positive and gram-negative organisms like *Streptococci*, *Staphylococci*, *Gonococci*, *Meningococci*, *H. influenza*, *Brucella*, *V. cholerae*, *Campylobacter*, *Y. pestis* and many anaerobes. They also inhibit rickettsiae, chlamydiae, mycoplasma, actinomyces, *E. histolytica* and

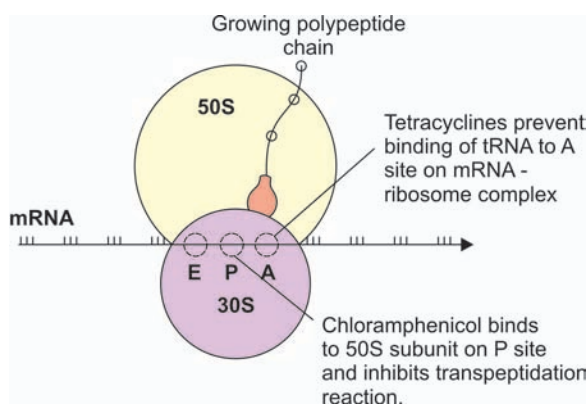


Fig. 38.1 : Mechanism of action of tetracyclines and chloramphenicol

plasmodia. Many organisms have now become resistant.

Pharmacokinetics Older tetracyclines are incompletely absorbed from the gut; food interferes with their absorption. Doxycycline - 95% and minocycline is 100% absorbed and food does not affect the absorption of these two agents. Tetracyclines chelate calcium and other metals which reduce their absorption. Hence tetracyclines should not be given with milk, iron preparations and antacids.

Tetracyclines except doxycycline and minocycline are excreted through kidneys. Doxycycline and minocycline are excreted through the gut and are therefore safe in renal insufficiency. For dosage of tetracyclines see Table 38.1.

Table 38.1: Dosage of some tetracyclines

<i>Tetracyclines</i>	<i>Doses</i>
Chlortetracycline (AUREOMYCIN)	250-500 mg QID
Tetracycline (HOSTACYCLINE)	250-500 mg QID
Doxycycline (DOXYCAPS)	200 mg initially then 100 mg OD
Minocycline (CYANOMYCIN)	200 mg initially then 100 mg OD

Adverse Effects

1. *GIT* Gastrointestinal irritation, nausea, vomiting and diarrhoea—tetracyclines are to be given with food to minimise these effects.
2. *Hepatotoxicity* may result in jaundice. Acute hepatic necrosis may occur in pregnant women but is rare.
3. *Renal toxicity* Renal failure may be aggravated. Outdated tetracyclines cause a syndrome like Fanconi's syndrome with vomiting, polyuria, proteinuria, glycosuria and acidosis due to the metabolites of outdated tetracyclines.
4. *Phototoxicity* Skin reactions and dermatitis on exposure to sun are more likely with doxycycline and demeclocycline.
5. *Effect on teeth and bones* Tetracyclines chelate calcium. The calcium - tetracycline - orthophosphate complexes get deposited in the developing teeth and bones. The deformities depend on the time of tetracycline administration as given below (Table 38.2) Tetracyclines are thus teratogenic.

6. *Suprainfections* Since the intestinal flora are extensively suppressed by tetracyclines, these are the most common antibiotics to cause superinfections.
7. *Hypersensitivity reactions* are not very common.

Uses

- A. *Tetracyclines are the drugs of choice in*
1. *Rickettsial infections* All rickettsial infections respond to tetracyclines.
 2. *Chlamydial infections*:
 - lymphogranuloma venereum—tetracyclines given for 2 weeks
 - trachoma—both topical and oral tetracyclines are needed
 - inclusion conjunctivitis.
 3. *Atypical pneumonia* due to *Mycoplasma pneumoniae*.
 4. *Cholera* Tetracyclines reduce the duration of illness and are of adjuvant value.
 5. *Brucellosis* Doxycycline 200 mg + Rifampicin 600 mg daily for 6 weeks is the treatment of choice.

Table 38.2: Teratogenic effects of tetracyclines

<i>Period</i>	<i>Structure affected</i>	<i>Deformity</i>
• Mid pregnancy to 5 months of postnatal life	Deciduous teeth	Brownish discolouration, ill formed and are more susceptible to caries
• 2 months to 5 years of age	Permanent teeth	Pigmentation, discolouration
• Pregnancy and childhood up to 8 years of age	Skeleton	Depressed bone growth

6. *Plague* Tetracyclines may be combined with an aminoglycoside.
- B. *Tetracyclines are useful in other infections like*
1. Periodontitis—In chronic periodontitis that does not respond to usual line of treatment, many modalities of treatment including surgery are used in order to reduce the number of microorganisms infecting the periodontium. Low dose tetracyclines (250mg q.i.d.) are used as adjuvants. 20 mg doxycycline given twice daily for 2-4 weeks is thought to act by inhibiting crevicular bacterial collagenases. These enzymes are thought to be responsible for the inflammation and injury to the periodontium - collagenases are dependent on calcium. By chelating Ca^{++} , tetracyclines suppress the collagenase activity and thereby suppress inflammation. Doxycycline polymer gel is now available in some countries - to be placed into the periodontal pocket so that the drug gets slowly absorbed. For systemic antibacterial activity tetracyclines may be combined with metronidazole or ciprofloxacin.
 2. Traveller's diarrhoea—Doxycycline reduces the incidence of traveller's diarrhoea.
 3. Sexually transmitted diseases like syphilis, gonorrhea and chancroid also respond to tetracyclines—but are not preferred.
 4. Acne—The propioni bacteria in the sebaceous follicles metabolise lipids into irritating free fatty acids which trigger the development of acne. Tetracyclines inhibit these bacteria. Low doses are given for a long time (250 mg BD for 4 weeks).
 5. Protozoal infections:
 - Amoebiasis—Tetracyclines are useful in chronic intestinal amoebiasis (page 321)
 - Malaria—Doxycycline is given with quinine in multi-drug resistant malaria.
 - C. *Inappropriate secretion of ADH* Demeclocycline is used because it inhibits the action of ADH in the kidney.

Contraindications Tetracyclines are contraindicated in pregnancy, lactation and in children up to 8 years of age.

Doxycycline (Table 38.3) and *minocycline* are semisynthetic tetracyclines.

- given orally they are 95 and 100% absorbed respectively
- food does not interfere with their absorption
- have long $t_{1/2}$ —can be given once daily
- excreted through gut hence can be given in usual dose even in the presence of renal impairment
- minocycline causes vestibular toxicity characterised by vertigo, dizziness, ataxia, nausea and vomiting.

Table 38.3: Compare and contrast tetracycline and doxycycline

Feature	Tetracycline	Doxycycline
1. Source	Semisynthetic	Semisynthetic
2. Intestinal absorption	Incomplete	Complete
3. Bioavailability	75%	95%
4. Lipid solubility	Low	High
5. Plasma $t_{1/2}$	8-10 hrs	18-24 hrs
6. Dose and frequency of administration	500mg QID	200mg stat, 100 mg O.D. from day 2
7. Route of excretion	Kidney	Gut
8. Safety in renal impairment	Not safe	Safe
9. Inhibition of intestinal flora	Significant	Low
10. Phototoxicity	Low	high

CHLORAMPHENICOL

Chloramphenicol is a broad spectrum antibiotic first obtained from *Streptomyces venezuelae* in 1947.

Mechanism of action Chloramphenicol is bacteriostatic but to some organisms it is bactericidal. It binds to 50S ribosomal subunit and inhibits protein synthesis - by inhibiting transpeptidation reaction (Fig. 38.1).

Antibacterial spectrum is broad and includes gram-negative organisms, some gram-positive organisms, anaerobic bacteria, Rickettsiae, Chlamydiae and *Mycoplasma*. Thus *H. influenzae*, *Salmonella*, *Shigella*, *Bordetella*, *Brucella*, gonococci, meningococci, streptococci, staphylococci, *Clostridium*, *E. coli* and *Klebsiella*—are inhibited apart from Rickettsiae, Chlamydiae and *Mycoplasma*.

Resistance is plasmid mediated and may be due to:

1. Inactivating enzymes
2. ↓ permeability of the microorganisms
3. Ribosomal insensitivity.

Pharmacokinetics Chloramphenicol is rapidly absorbed from the gut; penetration into tissues is excellent; attains high concentration in CSF. It is metabolised in the liver by conjugation.

Adverse Reactions

1. **Gastrointestinal disturbances** Nausea, vomiting, diarrhoea.
2. **Bone marrow depression** Chloramphenicol may cause bone marrow depression in two ways:
 - (i) dose dependent anaemia, leukopenia and thrombocytopenia due to inhibition of protein synthesis. It is reversible.
 - (ii) idiosyncratic response—resulting in aplastic anaemia which may be fatal. It may be due to a toxic metabolite. Incidence is 1 in 30,000 patients and occurs in genetically predisposed individuals. This toxicity has limited the use of chloramphenicol.

3. **Gray baby syndrome** Newborn babies given high doses of chloramphenicol may develop vomiting, refusal of feeds, hypotonia, hypothermia, abdominal distension, metabolic acidosis and ashen gray cyanosis—described as gray baby syndrome. It may be fatal. As the newborn cannot metabolize (due to inadequate hepatic glucuronidation) and excrete chloramphenicol adequately, toxicity results.
4. **Hypersensitivity reactions** like rashes and fever are uncommon.
5. **Superinfection** can occur.

Drug Interactions

Chloramphenicol inhibits hepatic microsomal enzymes and thereby prolongs the half-life of drugs metabolised by this system. This may result in enhanced toxicity of some drugs like phenytoin, tolbutamide and dicumarol.

Uses

Because of the risk of bone marrow toxicity and availability of safer drugs, chloramphenicol is not generally preferred either in dentistry or general medicine. The indications are:

1. **Typhoid fever** Very effective in typhoid; given for 14 days (500 mg QID till fever subsides then 250 mg QID up to 14th day).
2. **Bacterial meningitis** In meningococcal and *H. influenzae* meningitis—chloramphenicol is an alternative to penicillin.
3. **Anaerobic infections** Chloramphenicol + penicillin + an aminoglycoside can be used in severe anaerobic infections as an alternative to metronidazole and clindamycin.
4. **Rickettsial infections** As an alternative when tetracyclines are contraindicated.
5. **Eye infections** Chloramphenicol is used topically because of the good penetration into aqueous humour.

Aminoglycosides

Aminoglycosides are antibiotics with amino sugars in glycosidic linkages. They are derived from the soil actinomycetes of the genus streptomyces (streptomycin, kanamycin, tobramycin, neomycin) and the genus micromonospora (gentamicin and netilmicin) - hence the difference in spelling. Amikacin and netilmicin are semisynthetic products.

Common Properties of Aminoglycosides

1. Aminoglycosides are not absorbed orally (as they ionize in solution) therefore they are given parenterally.
2. They remain extracellularly and penetration into CSF is very poor.
3. They are excreted unchanged by the kidneys.
4. They are all bactericidal.
5. They act by inhibiting bacterial protein synthesis.
6. They are mainly effective against gram-negative organisms.
7. They produce variable degrees of ototoxicity and nephrotoxicity as adverse effects.

Antibacterial spectrum Aminoglycosides have a narrow spectrum and are effective mainly against aerobic gram-negative bacilli like *E. coli*, *Proteus*, *Pseudomonas*, *Brucella*, *Salmonella*, *Shigella* and *Klebsiella*.

Mechanism of action Aminoglycosides, being water-soluble penetrate the bacterial cell membrane through aqueous pores and from

there they are taken up by an active transport process. Inside the cell, (Fig. 39.1) aminoglycosides bind to 30S ribosomes and inhibit bacterial protein synthesis - block initiation of protein synthesis, cause termination of protein synthesis and cause addition of incorrect amino acids resulting in the synthesis of abnormal proteins. Aminoglycosides are *bactericidal*. Higher the concentration, greater is the bactericidal effect. A residual bactericidal effect—*postantibiotic effect*—remains even after the plasma levels of aminoglycosides fall. Hence, even though they have a short $t_{1/2}$, they can be given once a day (Table 39.1).

Resistance to aminoglycosides is acquired by

1. Aminoglycoside inactivating enzymes.
 2. Low affinity of ribosomes - acquired by mutation.
 3. Decrease in permeability to the antibiotic.
- There is partial cross-resistance among various aminoglycosides.

Pharmacokinetics

Aminoglycosides are not absorbed from the gut but when instilled into body cavities or applied over large wounds, they may get rapidly absorbed. Following IM injection peak levels are seen in 60 minutes. They are not bound to plasma proteins and do not enter cells or cross barriers - mostly remain in the vasculature. In patients with severe

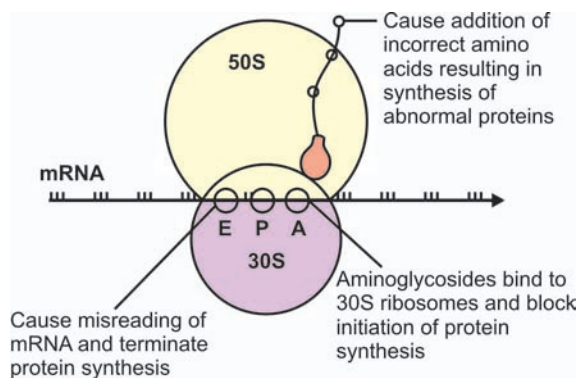


Fig. 39.1: Mechanism of action of aminoglycosides

infection, plasma concentration of aminoglycosides should be determined to guide the treatment.

Adverse Effects

1. **Ototoxicity** is the most important toxicity. Both vestibular and auditory dysfunction can occur depending on the dose and duration. The aminoglycosides get concentrated in the labyrinthine fluid of the inner ear and damage both cochlear hair cells and vestibular sensory cells. As the cochlear cells cannot regenerate, there is progressive, *permanent deafness*. The auditory nerve degenerates. Tinnitus appears first, followed by deafness; elderly people are more susceptible.

Stopping the drug can prevent further damage. Vestibular dysfunction is manifested by headache, nausea, vomiting, dizziness, vertigo, nystagmus and ataxia. Most symptoms subside in two weeks except ataxia which may persist for 1-2 years.

2. **Nephrotoxicity** Aminoglycosides attain high concentration in the renal cortex and cause damage to the renal tubules. This results in loss of urine concentrating capacity, low GFR and albuminuria. These effects are reversible. Most symptoms subside in 2 weeks except ataxia which may persist for 1-2 years.
3. **Neuromuscular blockade** Aminoglycosides have curare-like effects and block neuromuscular transmission.

Precautions in Using Aminoglycosides

1. Avoid concurrent use of other ototoxic drugs like loop diuretics.
2. Avoid concurrent use of other nephrotoxic drugs like amphotericin B, cephalothin and cisplatin.
3. Avoid concurrent use of curarimimetic drugs.
4. To be used cautiously in elderly, in renal damage and in combination with skeletal muscle relaxants.
5. Contraindicated in pregnancy because of risk of deafness in the child.

Table 39.1: Dose and routes of administration of aminoglycosides

Aminoglycosides	Doses	Routes
Streptomycin (STREPTONEX)	1-2 g/day	IM
Gentamicin (GARAMYCIN)	3-5 mg/kg/day in 3 divided doses	IM/IV
Tobramycin (TOBRANEG)	3-5 mg/kg/day in 3 divided doses	IM/IV
Amikacin (AMICIN)	15 mg/kg/day in 2-3 divided doses	IM/IV
Netilmicin (NETROMYCIN)	4-6 mg/kg/day in 2-3 divided doses	IM/IV

6. Do not mix aminoglycosides with any other drug in the same syringe.
7. Determination of plasma levels of aminoglycosides may be needed in severe infections and in patients with renal dysfunction.

Streptomycin obtained from *Streptomyces griseus* is mainly effective against aerobic gram-negative bacilli. When used alone, bacteria, especially the tubercle bacillus rapidly develops resistance to it. Streptomycin is the least nephrotoxic among aminoglycosides.

Uses

1. *Tuberculosis*
2. *Subacute bacterial endocarditis (SBE)*—Combination of streptomycin and penicillin is synergistic in this condition.
3. *Plague, tularaemia and Brucellosis*—Streptomycin is given with a tetracycline.

Gentamicin obtained from *Micromonospora purpurea* (Table 39.2) is more potent and has a broader spectrum of action compared to streptomycin. Development of resistance has limited its use.

Uses

1. *UTI* Gentamicin is effective in uncomplicated UTI as it is released for a long time from the renal cortex.
2. *Pneumonia* due to gram-negative organisms may be treated with gentamicin + penicillin.
3. *Osteomyelitis, peritonitis, septicæmia* caused by gram-negative organisms can be treated with gentamicin.
4. *Meningitis due to gram-negative bacilli*—gentamicin is used with a III generation cephalosporin.
5. Gentamicin may be used in place of streptomycin in SBE.
6. *Topical*
 - Gentamicin cream is used topically in burns and other infected wounds.
 - Gentamicin eye drops are used in the prevention and treatment of bacterial conjunctivitis.

Tobramycin has better activity against *Pseudomonas* and is used with an antipseudomonal penicillin in such infections.

Table 39.2: Compare and contrast amoxicillin and gentamicin

Features	Amoxicillin	Gentamicin
Chemistry	β lactam antibiotic	Aminoglycoside
Source	Semisynthetic	Natural from <i>Micromonospora purpurea</i>
Antibacterial spectrum	Wide - Gm+ve and Gm-ve microorganisms	Narrow – mostly Gm-ve microorganisms.
Mechanism of action	Inhibits cell wall synthesis	Inhibits protein synthesis.
Intestinal absorption	Well absorbed	Not absorbed
Route of administration	Oral	Parenteral
Volume of distribution	Large	Small
Therapeutic index	High	Low
Prominent adverse effects	Diarrhoea, allergy	Ototoxicity, Nephrotoxicity
Major action	• Antibiotic • Bactericidal	• Antibiotic • Bactericidal

Gm+ve-gram positive Gm-ve- gram negative

Antibiotics that inhibit protein synthesis bind to ribosomes

50S	30S
Erythromycin	Tetracyclines
Chloramphenicol	Aminoglycosides
Clindamycin	
Streptogramins	
Linezolid	

Kanamycin Due to its toxicity, its use is limited to multi-drug resistant tuberculosis. **Amikacin** has widest antibacterial spectrum among the aminoglycosides. It is resistant to aminoglycoside inactivating enzymes.

Uses

1. Nosocomial infections due to gram-negative organisms
2. Tuberculosis—Amikacin is useful in multidrug resistant tuberculosis in combination with other drugs. It is also used in infections due to *atypical mycobacteria* in patients with AIDS.

Netilmicin Like amikacin, netilmicin is resistant to aminoglycoside inactivating enzymes. It is used in serious infections due to gram-negative bacilli.

Sisomicin has actions, toxicity and uses similar to gentamicin.

Neomycin has a wide antibacterial spectrum. As it is highly ototoxic, it is not given systemically. It is used topically as ointments, creams and powder.

Adverse effects Neomycin can cause skin rashes on topical use. Oral use can cause diarrhoea, steatorrhoea and malabsorption due to damage to the intestinal villi. Superinfection with *Candida* can also occur.

Uses

1. Neomycin is used topically in skin infections, burns, ulcers and wounds; eye and ear infections.
2. Orally—neomycin is not absorbed when given orally. It is used to prepare the bowel for surgery, i.e. for preoperative gut sterilization.
3. Hepatic coma—ammonia produced by colonic bacteria is absorbed and converted to urea by the liver. In severe hepatic failure, as liver is unable to handle this NH_3 , blood NH_3 levels rise resulting in encephalopathy. As neomycin inhibits intestinal flora, NH_3 production falls. Neomycin is given orally for this purpose.

Macrolides, Other Antibacterial Agents and Chemotherapy of Urinary Tract Infections

Macrolides are antibiotics with a macrocyclic lactone ring to which sugars are attached. Erythromycin and its semisynthetic derivatives roxithromycin, clarithromycin and azithromycin are macrolides.

ERYTHROMYCIN

Erythromycin is obtained from *Streptomyces erythreus*.

Antibacterial spectrum Erythromycin has a narrow spectrum and is effective against aerobic gram-positive bacteria and a few gram-negative organisms.

Streptococci, pneumococci, staphylococci, gonococci, *C. diphtheriae*, *C. jejuni*, *Mycoplasma*, *Chlamydiae* and some atypical mycobacteria are sensitive.

Mechanism of Action

Erythromycin is bacteriostatic at low and cidal at high concentrations. It binds to 50S ribosomes (Fig. 40.1) and inhibits bacterial protein synthesis. Chloramphenicol and clindamycin also bind to 50 S ribosomes and the three may inhibit each others activity. Hence the combination should be avoided.

Resistance Resistance to macrolides is acquired through plasmids. The mechanism involved may be:

- Low permeability of the bacteria to the antibiotic
- Production of inactivating enzymes
- Low affinity of ribosomes to macrolides.

Pharmacokinetics Erythromycin is destroyed by gastric acid and is therefore given as enteric coated tablets. Good concentration is attained in most fluids except brain and CSF. It is mainly excreted through bile; dose adjustment is not needed in renal failure. For dose and duration of treatment with macrolide antibiotics see Table 40.1.

Adverse Effects

1. Hepatitis with cholestatic jaundice starts after 2-3 weeks of treatment and is more common with the estolate salt. The symptoms—nausea, vomiting and abdominal cramps, mimic acute cholecystitis and may be wrongly treated. These are followed by jaundice and fever. It may be an allergic response to the estolate salt. The patient recovers on stopping the drug.

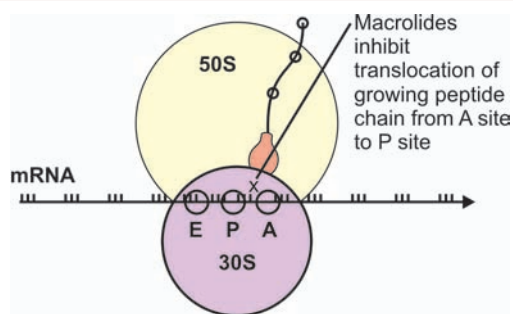


Fig. 40.1: Mechanism of action of macrolide antibiotics

2. Epigastric distress, nausea, vomiting and diarrhoea are often reported. Erythromycin is a motilin receptor agonist due to which it causes increased intestinal motility.
3. Allergic reactions including fever and skin rashes can occur.
4. Cardiac arrhythmias are reported in patients with cardiac diseases or on other arrhythmogenic drugs.
5. Erythromycin can also cause reversible hearing impairment in some patients.

Drug Interactions Erythromycin and clarithromycin inhibit the hepatic metabolism and

thereby raise the plasma levels of carbamazepine, terfenadine, theophylline, valproate, digoxin and warfarin resulting in toxicity due to these drugs.

Uses

Erythromycin can be used as an alternative to penicillin in patients allergic to penicillin.

1. *Oral infections*—Erythromycin is quite commonly used in the prevention and treatment of oral infections including post-extraction infections, periapical abscesses and other infected periodontal lesions. It is also the preferred antibiotic in patients allergic to penicillins.
2. *Atypical pneumonia* may be caused by agents like Mycoplasma, Chlamydia and Legionella. Atypical pneumonia due to *Mycoplasma pneumoniae*—erythromycin is the *drug of choice*- 500 mg 6 hrly oral or IV.
3. *Legionnaire's pneumonia*—is treated for 10-14 days with erythromycin. IV erythromycin is preferred. Azithromycin is now considered the drug of choice.

Table 40.1: Adult dose and duration of treatment with macrolide antibiotics

Drug	Dose (oral) and duration
Erythromycin stearate (ERYTHROCIN)	250-500 mg QID 7-14 days
Erythromycin estolate (ALTHROCIN)	250-500 mg QID 7-14 days
Erythromycin gluceptate	500-1000 mg 6 hrly for 10-14 days
Roxithromycin (ROXID)	150 mg BD (to be taken 30 minutes before food)
Clarithromycin (CLARIBID)	250-500 mg BD 7-14 days
Azithromycin (AZITHRAL)	1st day 500 mg OD 250 mg OD for next 3-4 days (to be taken 1 hr before or 2 hrs after food)

4. *Whooping cough*—erythromycin is the drug of choice for the treatment and post-exposure prophylaxis of close contacts. Clarithromycin and azithromycin may also be used.
 5. *Streptococcal infections*—pharyngitis, tonsillitis and scarlet fever respond to erythromycin.
 6. *Staphylococcal infections*—minor infections may be treated. But now resistant strains are common (Table 40.2).
 7. *Diphtheria*—erythromycin is very effective in acute stage though antitoxin is life saving. Erythromycin also eradicates carrier state.
 8. *Syphilis and gonorrhoea*—erythromycin is used as an alternative to penicillins.
 9. *Campylobacter gastroenteritis*—as an alternative to fluoroquinolones.
 10. *Tetanus*—erythromycin eradicates carrier state.
 11. *Anthrax*—erythromycin is an alternative to penicillin.
 12. *Topical*—erythromycin ointment is used for skin infections and boils. Lotion is used for acne vulgaris.
- Roxithromycin* is longer-acting, acid stable, more potent, better absorbed and has better tissue penetrability compared to erythromycin. It does not inhibit the metabolism of

Table 40.2: Preferred drugs in some infections

Drugs used in MRSA*	<i>Pseudomonas aeruginosa</i>
• Vancomycin • Teicoplanin • Quinupristin-dalfopristin • Linezolid • Rifampicin	• Antipseudomonal penicillin + tobramycin • Ceftazidime or cefepime • Antipseudomonal penicillin + ciprofloxacin • Imipenem/meropenem+tobramycin • Aztreonam + tobramycin

* Methicillin - Resistant *Staphylococcus aureus*

Anaerobic infections

- Metronidazole
- Clindamycin
- Chloramphenicol
- Cefotaxime, ceftizoxime, cefotetan
- Imipenem
- Ampicillin + Sulbactam
- Piperacillin + Tazobactam

Atypical mycobacteria

- Clarithromycin + ethambutol
- Rifabutin + ethambutol + ciprofloxacin
- Amikacin

Toxoplasma gondii

- Pyrimethamine + Sulfadiazine + folinic acid
- Spiramycin
- Pyrimethamine + clindamycin

other drugs—hence drug interactions are avoided. It should be taken 30 min before food.

It can be used as an alternative to erythromycin but is more expensive. Roxithromycin is quite a popular antibiotic because of its advantages over erythromycin. It is used in orodental infections apart from other indications of erythromycin.

Clarithromycin Compared to erythromycin, clarithromycin is longer-acting, acid stable and better absorbed; it is more effective against atypical mycobacteria, *H. pylori* and some protozoa. Clarithromycin is structurally similar to erythromycin and therefore its drug interactions are also similar to erythromycin.

Clarithromycin is used:

1. As a component of triple regimen for *H. pylori* infections in peptic ulcer patients.
2. Atypical mycobacterial infections.

Though clarithromycin is effective in other indications of erythromycin, its higher cost makes it less preferable.

Azithromycin an azalide, is a derivative of erythromycin with activity similar to clarithromycin. It is acid stable, rapidly absorbed, has better tissue penetrability, is longer acting and better tolerated than erythromycin. It is given as a single loading dose of 500 mg followed by 250 mg for the next 4 days. Azithromycin is free of drug interactions as it does not suppress hepatic metabolism of other drugs.

It is used in the prophylaxis and treatment of atypical mycobacterial infections in AIDS patients. Like erythromycin it can also be used in respiratory, genital and skin infections and in pneumonias.

KETOLIDES are modified macrolides that are similar to newer macrolides except that they are effective against macrolide - resistant pneumococci. *Telithromycin* is a ketolide.

MISCELLANEOUS ANTIBIOTICS

Spectinomycin is related to aminoglycosides and is effective against gram-negative bacteria. It is used only in gonorrhoea (2 gm IM) in patients allergic to penicillin and quinolones.

Lincosamides

Lincomycin and clindamycin are (Table 40.3) lincosamides. Lincomycin is no longer used clinically.

Clindamycin is a congener of lincomycin. It binds to 50S ribosomal subunit and suppresses protein synthesis. Streptococci, staphylococci, pneumococci and many anaerobes are inhibited by clindamycin. Clindamycin is well-absorbed on oral administration. It attains good concentration in the bone and many other tissues. It is metabolised in the liver.

Adverse effects include diarrhoea due to pseudomembranous colitis, skin rashes and neuromuscular blockade. Intravenous use can cause thrombophlebitis.

Uses Anaerobic infections—abdominal, pelvic, bone and joints infections due to anaerobes are treated with clindamycin. It may be combined with an aminoglycoside or a cephalosporin.

Clindamycin is also useful in *Pneumocystis carinii* pneumonia and toxoplasmosis in AIDS patients.

GLYCOPEPTIDES

Vancomycin and teicoplanin are glycopeptides. (Table 40.2) Vancomycin produced by *Streptococcus orientalis* is active against gram-positive bacteria particularly staphylococci including those resistant to methicillin. It acts by inhibiting cell wall synthesis and is bactericidal. Vancomycin is not absorbed orally—given IV. It is widely distributed and excreted through kidneys.

Adverse effects are skin rashes, pain at the site of injection, thrombophlebitis, ototoxicity and nephrotoxicity. Concurrent use of other ototoxic and nephrotoxic drugs should be avoided; dose should be adjusted in renal dysfunction.

Uses

1. Pseudomembranous colitis—oral vancomycin is used.
2. Methicillin resistant staphylococci—vancomycin is given IV for serious infections like osteomyelitis, endocarditis and soft-tissue abscesses.
3. Enterococcal endocarditis—as an alternative to penicillin.
4. Penicillin resistant pneumococcal infections—vancomycin is recommended with a cephalosporin.

Teicoplanin has mechanism of action and antibacterial spectrum similar to vancomycin, but teicoplanin can be safely given intramuscularly. It is also less toxic. Occasionally causes allergic reactions. It is used in osteomyelitis and endocarditis due to methicillin resistant staphylococci and enterococci. TARGOCID 200-400 mg/day.

POLYPEPTIDE ANTIBIOTICS

Polymyxin and Colistin are too toxic to be given systemically. They are used topically. Polymyxin obtained from *Bacillus polymyxa* and colistin from *Bacillus colistinus* are effective against gram-negative bacteria.

Mechanism of action Polymyxin and colistin alter the permeability of the cell membrane resulting in leakage of the cell contents. They are bactericidal.

Polypeptide antibiotics are not absorbed orally; applied topically, they may rarely cause skin rashes.

Uses

1. Used topically for skin infections, ear and eye infections.
2. Oral colistin is used in children for diarrhoea due to gram-negative bacilli.

OTHER ANTIMICROBIAL AGENTS

Bacitracin produced by *Bacillus subtilis* is effective against gram-positive bacteria. It inhibits the cell wall synthesis and is bactericidal. It is too toxic to be given systemically, not absorbed orally and is therefore used only for topical application—in skin infections, surgical wounds, ulcers and ocular infections (NEOSPORIN powder is bacitracin + neomycin).

Sodium Fusidate (Fusidic acid) obtained from *Fusidium coccineum* is effective against gram-positive organisms particularly staphylococci. It is bactericidal. It is mainly used topically as a 2% ointment (FUCIDIN). It may be given orally for resistant staphylococcal infections. *Mupirocin* or pseudomonic acid is obtained from *Pseudomonas fluorescens*. It is bactericidal against gram-positive and some gram-negative organisms including methicillin resistant *Staphylococcus aureus*. Mupirocin acts by inhibiting the enzyme tRNA synthetase. It is used as a 2% ointment (BACTROBAN) for minor skin infections particularly due to staphylococci and streptococci. It is also used intranasally as spray to eradicate staphylococcal carrier state.

Fosfomycin is an analog of phosphoenol pyruvate. Fosfomycin is effective against both gram-positive and gram-negative organisms. It acts by inhibiting the enzyme endopyruvate transferase. This enzyme is required for the first step in bacterial cell wall synthesis. Thus it inhibits bacterial cell wall synthesis. The salt used is fosfomycin tetrametol which is available for both oral

and parenteral use. It is excreted by the kidneys and attains high concentration in the urine. Fosfomycin is approved for use in uncomplicated lower UTI in women - single 3G dose is effective.

Cycloserine obtained from *Streptomyces orchidaceus* inhibits many gram-positive and gram-negative organisms including *M. tuberculosis*. It acts by inhibiting protein synthesis and is used as a second line drug in tuberculosis (see page 294).

Newer Agents

Streptogramins quinupristin and dalfopristin are obtained from *Streptomyces pristinaspiralis*. A combination of *quinupristin* and *dalfopristin* in the ratio 30:70 is bactericidal against gram-positive cocci including methicillin-resistant staphylococci.

Mechanism of action Streptogramins bind to 50S ribosomal subunit and inhibit protein synthesis.

Given intravenously, streptogramins are rapidly metabolised and excreted largely through faeces. Hence adjustment of dose is not required in renal insufficiency. Adverse effects include arthralgia, myalgia, nausea, vomiting, diarrhoea and pain at the site of injection. The combination is used intravenously in the treatment of infections due to streptococci, methicillin-resistant staphylococci and enterococci. Streptogramins are not effective orally as they are rapidly metabolised in the liver - undergo extensive first pass metabolism.

Oxazolidinones

Linezolid is an oxazolidinone effective against gram-positive bacteria including methicillin resistant staphylococci and gram-positive anaerobic organisms. It acts by inhibiting protein synthesis on binding to 50S ribosomes. Adverse effects include

nausea, diarrhoea, dizziness and thrombocytopenia. It can be given orally or IV. Linezolid is useful in the treatment of nosocomial infections resistant to other drugs.

Nitroimidazoles

Nitroimidazoles include metronidazole, tinidazole, secnidazole, ornidazole and satranidazole. They are very effective in the treatment of anaerobic microorganisms apart from amoebiasis. They are discussed under antiamoebic drugs (see page 321).

CHEMOTHERAPY OF URINARY TRACT INFECTION

Infection of the urinary tract is quite common and may be acute or chronic. *Urinary antiseptics* are drugs which exert antibacterial activity only in the urinary tract (and no systemic activity). They include nitrofurantoin and methenamine mandelate.

Nitrofurantoin is bacteriostatic, but at higher concentrations it may be bactericidal. It is a synthetic compound, effective against many gram-positive and gram-negative bacteria. Mechanism of action is not known. It is rapidly and completely absorbed from the gut. It attains high concentration in urine and is used in acute UTI, long-term suppression of chronic UTI (single dose 100 mg at bed time) and for prophylaxis of UTI. It may cause nausea, vomiting, diarrhoea and allergic reactions. Development of resistance is rare. Dose 50 - 100 mg 6 hrly (FURADANTIN).

Methenamine mandelate—a salt of mandelic acid and methenamine, releases formaldehyde in acidic urine below pH 5.5. Formaldehyde is bactericidal and resistance does not develop to it.

High doses can cause nausea, epigastric distress, haematuria and painful micturition.

Table 40.3: Antimicrobial agents

β -lactam antibiotics	Quinolones	Sulphanomides	Macrolides
<i>Penicillins</i> - Benzyl penicillin - Ampicillin - Amoxicillin - Methicillin - Cloxacillin - Nafcillin - Carbenicillin - Ticarillin - Azlocillin - Piperacillin <i>Cephalosporins</i>: - Cephalexin - Cephazolin - Cefuroxime - Cefachlor - Ceftriaxone - Ceftazidime - Cefpirome - Cefepime <i>Carbapenems</i> - Imipenem - Meropenem - Ertapenem <i>Carbacephem</i> - Loracarbef <i>Monobactams</i> - Aztreonam	- Nalidixic acid - Cinoxacin - Oxalinic acid <i>Fluoroquinolones</i> - Ciprofloxacin - Norfloxacin - Ofloxacin - Sparfloxacin - Trovafloxacin <i>Newer agents</i> - Streptogramins - Quinupristin + Dalfopristin - Oxazolidinones - Linezolid	- Sulfisoxazole - Sulfadiazine - Sulfadoxine - Sulfacetamide - Sulfasalazine <i>Cotrimoxazole</i> - Trimethaprim + Sulfamethoxazole <i>Miscellaneous</i> <i>Glycopeptides</i> - Vancomycin - Teicoplanin <i>Lincosamides</i> - Clindamycin <i>Polypeptides</i> - Polymyxin - colistin <i>Others</i> - Bacitracin - Sodium usidate - Mupirocin	- Erythromycin - Roxithromycin - Azithromycin - Clarithromycin <i>Ketolides</i> - Telithromycin <i>Aminoglycosides</i> - Gentamycin - Streptomycin - Neomycin - Amikacin - Netilmicin - Sisomicin <i>Broad spectrum Antibiotics</i> - Chloramphenicol - Tetracycline - Oxytetracycline - Demeclocycline - Doxycycline - Minocycline

Drug Interactions

Methenamine binds sulfonamides and neutralises their action. Also, sulfonamides are precipitated in the acidic urine. Hence the combination should be avoided.

Uses

Methenamine mandelate is used orally in chronic UTI that is resistant to other drugs.

Other drugs used in UTI are sulfonamides, cotrimoxazole, nalidixic acid, fluoroquinolones, ampicillin, cloxacillin, carbenicillin, aminoglycosides, tetracyclines and cephalosporins.

Urinary analgesic—phenazopyridine has analgesic actions on the urinary tract and relieves burning symptoms of dysuria and urgency.

41

Chemotherapy of Tuberculosis and Leprosy

Tuberculosis is a chronic granulomatous disease caused by *Mycobacterium tuberculosis*. In developing countries, it is a major public health problem; 5 lakh people die in India every year due to this disease. After the spread of AIDS, the problem has become more complex, as tuberculosis and *Mycobacterium avium* complex (MAC) infections are more common and rapidly progress in these patients.

Drugs Used in Tuberculosis

- **First line drugs** Isoniazid, rifampicin, pyrazinamide, ethambutol, streptomycin.
- **Second line drugs** Ethionamide, thiacetazone, para aminosalicylic acid (PAS), amikacin, ciprofloxacin, capreomycin, cycloserine, rifabutin, kanamycin.

Based on antitubercular activity, drugs may be grouped as:

- **Tuberculocidal agents**—Isoniazid, rifampicin, streptomycin, pyrazinamide, capreomycin, kanamycin, ciprofloxacin.
- **Tuberculostatic agents**—Ethambutol, ethionamide, thiacetazone, cycloserine PAS.

First Line Drugs

Isoniazid

Isoniazid (INH) is the most effective and cheapest primary antitubercular drug. It is

tuberculocidal for rapidly multiplying bacilli but static for resting bacilli. INH destroys:

- (i) intracellular bacilli as it penetrates into the cells, i.e. tubercle bacilli in macrophages, and
- (ii) bacilli multiplying in the walls of the cavities. Thus it is effective against both intra and extracellular organisms (Fig. 41.1, Table 41.2). If used alone, mycobacteria develop resistance to it. Hence it should be used in combination with other drugs.

Mechanism of action INH inhibits the synthesis of mycolic acids which are the important components of the mycobacterial cell wall.

INH enters the mycobacteria where it is converted to an active metabolite. This metabolite binds the enzymes necessary for mycolic acid synthesis. Thus the synthesis of mycolic acid is inhibited.

Pharmacokinetics INH is completely absorbed orally, penetrates all tissues, tubercular cavities, necrotic tissues and CSF. It is metabolised by acetylation. Patients can be fast or slow acetylators depending on the genetic inheritance - slow acetylators respond better. The $t_{1/2}$ in slow acetylators is 3-5 hours while in fast acetylators it is 1 hour. Peripheral neuropathy is more common in slow acetylators while hepatotoxicity is more likely in fast acetylators. Metabolites of INH are excreted in urine.

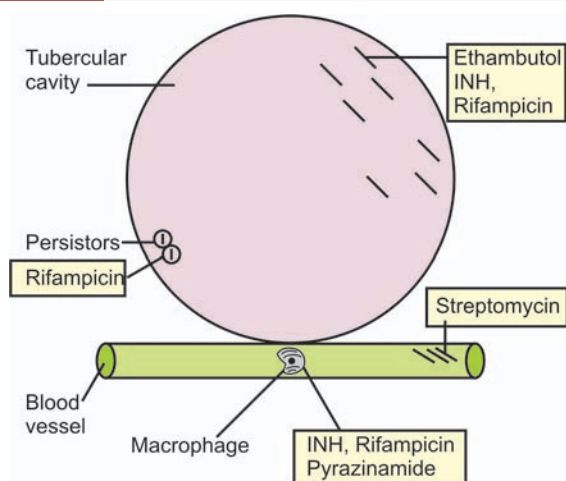


Fig 41.1 : Sites of action of antitubercular drugs

Adverse effects Peripheral neuritis (due to interference with utilization and increased excretion of pyridoxine) can be avoided by giving prophylactic pyridoxine (10-50 mg) with INH. Hepatitis is another major adverse effect, more common in alcoholics. It can cause CNS toxicity including psychosis and seizures but are less common - epileptics are more prone to this effect. Other minor effects like anorexia, gastrointestinal discomfort, fever and allergic reactions can occur. Haemolysis can occur in patients with G₆PD deficiency.

Rifampicin

Rifampicin (rifampin) is a semisynthetic derivative of rifamycin, an antibiotic obtained from *Streptomyces mediterranei*. The other rifamycins are rifabutin and rifapentine. Rifampicin is bactericidal to *M. tuberculosis*, *M. leprae* and atypical mycobacteria. It also inhibits most gram-positive and gram-negative bacteria like *Staph. aureus*, *N. meningitidis*, *E. coli*, *Proteus*, *Pseudomonas* and *Legionella*.

Antitubercular action Rifampicin is highly effective, tuberculocidal and is the only drug that acts on persisters; acts on both intra- and extracellular organisms and is effective against tubercle bacilli resistant to other drugs. If used alone resistance develops.

Mechanism of action Rifampicin binds to DNA dependent RNA polymerase and inhibits RNA synthesis in the bacteria.

Pharmacokinetics Rifampicin is well-absorbed and has good tissue penetrability—reaches caseous material, cavities and CSF; It also appears in saliva, tears and sweat. It is a microsomal enzyme inducer—hence can result in many drug interactions. See - Table 41.1 for doses of antitubercular drugs.

Adverse effects

1. Hepatotoxicity—Rifampicin can cause hepatitis. Patients receiving other hepatotoxic drugs or those with any liver dysfunction should be carefully monitored deaths have been reported in such patients.
2. Gastrointestinal disturbances—Epigastric distress, nausea, vomiting, abdominal cramps and diarrhoea can occur.
3. Flu-like syndrome—characterised by fever, bodyache, chills and haemolytic anaemia is more common in intermittent dosing regimen.
4. CNS symptoms—Including headache, drowsiness, dizziness, ataxia, confusion and peripheral neuropathy with pain and numbness in the extremities and muscle weakness have been reported.

Table 41.1: Recommended doses of antitubercular drugs

Drugs	Doses
Isoniazid (INH)	300-400 mg
Ethambutol (E)	800-1000 mg
Rifampicin (R)	450-600 mg
Streptomycin (S)	750-1000 mg
Pyrazinamide (Z)	1200-1500 mg
Thiacetazone (T)	150 mg

5. Hypersensitivity reactions—With fever, skin rashes and urticaria, rarely renal manifestations with nephritis, hemolysis, haematuria and renal insufficiency can occur.
6. Staining of secretions—Rifampicin stains the secretions including tears, saliva and sweat—an orange red colour and the patient should be informed about this.
5. Brucellosis - Rifampicin 600-900 mg + doxycycline 200 mg daily for 6 weeks - drug of choice.
6. To eradicate carrier state - rifampicin eradicates the nasal carrier state of *N. meningitidis*, *H. influenzae* and *S. aureus* - 600 mg BD for 2 days.

Rifabutin is similar to rifampicin except that it causes milder enzyme induction and is more active against atypical mycobacteria. Rifabutin may be used in place of rifampicin in tuberculosis patients with AIDS who are receiving antiretroviral drugs. These antiviral drugs are also metabolised by microsomal enzymes and rifampicin being a powerful enzyme inducer, can result in many drug interactions.

Rifapentine is an analog of rifampicin and is similar to it.

Uses

1. Tuberculosis and atypical mycobacterial infections.
2. Leprosy (see page 296).
3. Prophylaxis of *H. influenzae* and meningococcal meningitis in close contacts particularly children - 20 mg/kg/day for 4 days.
4. Resistant staphylococcal infections - rifampicin may be given in combination with a β lactam antibiotic or vancomycin.

Pyrazinamide

Pyrazinamide is tuberculocidal, being more active in acidic pH. Mechanism of action is

Table 41.2: Antitubercular actions and characteristic adverse effects of some antitubercular drugs

Drug	Antitubercular action	Serious toxicity
Isoniazid	Tuberculocidal; acts on intra- and extracellular organisms	Peripheral neuritis, seizures, psychosis
Rifampicin	Tuberculocidal; Acts on intra- and extracellular organisms, persists and drug resistant organisms	Hepatotoxicity, flu-like syndrome, nephritis; urine and secretions are coloured orange-red
Pyrazinamide	Tuberculocidal, kills intracellular organisms; more active in acidic pH	Hepatotoxicity, arthralgia, hyperuricaemia
Streptomycin	Tuberculocidal, acts on extracellular organisms	Ototoxicity, nephrotoxicity
Ethambutol	Tuberculostatic; inhibits tubercle bacilli in the walls of cavities	Optic neuritis with ↓ visual acuity and red-green colour blindness
Thiacetazone	Tuberculostatic; low efficacy; delays development of resistance to other drugs	Hepatotoxicity, dermatitis

not known. It is effective against intracellular bacilli. If used alone resistance develops. It is well-absorbed (achieves good concentration in CSF). Hepatotoxicity is the most common adverse effect. Hyperuricaemia (due to ↓ excretion of uric acid may result in gouty arthritis), arthralgia, anorexia, vomiting and rashes may be seen.

Streptomycin

Streptomycin (page 282) is tuberculocidal, acts only against extracellular organisms due to poor penetrating power. It has to be given IM. When used alone resistance develops. Because of these disadvantages and its toxicity (ototoxicity and nephrotoxicity), streptomycin is the least preferred of the first line drugs.

Second Line Drugs

Ethambutol is tuberculostatic and acts on fast multiplying bacilli in the cavities. It is also effective against atypical mycobacteria. It inhibits the incorporation of mycolic acids into the mycobacterial cell wall.

Optic neuritis resulting in ↓ visual acuity and inability to differentiate red from green is an important adverse effect which needs withdrawal of the drug. Colour vision should be monitored during treatment. Ethambutol is to be avoided in children because their ability to differentiate red from green cannot be reliably tested. Other adverse effects include nausea, anorexia, headache, fever and allergic reactions.

Thiacetazone is tuberculostatic with low efficacy; it delays the development of resistance to other drugs and its low cost makes it a suitable drug in combination regimens. Hepatotoxicity, dermatitis, allergic reactions and GI side effects may occur.

Ethionamide This tuberculostatic drug is effective against both intra- and extracellular

organisms. It is also effective in atypical mycobacteria.

Anorexia, nausea, vomiting and metallic taste in the mouth are the most common adverse effects. It can also cause hepatitis, skin rashes and peripheral neuritis (needs prophylactic pyridoxine).

Ethionamide is a secondary agent used only when primary drugs are ineffective.

Para-aminosalicylic acid (PAS) related to sulfonamides is tuberculostatic. Gastro-intestinal effects like nausea, anorexia, epigastric pain and diarrhoea make it a poorly tolerated drug. Allergic reactions and hepatitis are also seen. It is rarely used.

Other Second Line Drugs

Amikacin, *kanamycin* and *capreomycin* are second line drugs that need parenteral administration. They are ototoxic and nephrotoxic and are used only in resistant cases. Amikacin is also effective against atypical mycobacteria.

Cycloserine is an antibiotic that inhibits cell wall synthesis, is tuberculostatic and is also effective against some gram-positive organisms. It causes CNS toxicity including headache, tremors, psychosis and sometimes seizures. It is used only in resistant tuberculosis.

Fluoroquinolones Ciprofloxacin, ofloxacin and sparfloxacin inhibit tubercle bacilli and atypical mycobacteria. They are useful in multi-drug resistant tuberculosis in combination with other drugs.

Treatment of Tuberculosis

Tuberculosis is one of the most difficult infections to cure. The properties of the mycobacteria like slow division, development of resistance, ability to remain as persisters for years and intracellular location of the bacilli have enhanced the problem.

Moreover, the caseous material makes it difficult for the drugs to reach. The need for long-term treatment, drug toxicity, cost and thereby poor patient compliance have all added to further complicate the problem. But with the availability of effective drugs, most patients can now be treated as outpatients.

The aim of treatment is to kill the dividing bacilli thus making the patient sputum negative and to destroy the persisters in order to prevent relapse and ensure complete cure.

A combination of drugs is used in tuberculosis to -

1. delay the development of resistance
2. reduce toxicity
3. shorten the course of treatment.

Majority of cases are sensitive to first line drugs. Initial treatment should be intensive and include drugs that have maximum effect. Good patient compliance and cost of therapy should also be considered.

Chemotherapy is given in two phases-

- *First phase* - initial, intensive phase of 1-3 months duration aimed at killing as many bacilli as possible.
- *Second phase* - continuation phase to destroy the dormant or persisters - duration 6-9 months.

Short-term Regimens

1. INH + R + Z + E/S daily for 2 months followed by INH + R daily for 4 months.
2. INH + R + Z daily for 2 months followed by INH + R daily for 7 months.

Advantages

Short-term therapy has rapid response, lower failure rates, lesser chances of resistance and better patient compliance.

Conventional Regimen

- INH + S + T daily for 2 months
- INH + T daily for 10 months

Failure rates are high and compliance is poor.

Though many effective antitubercular drugs are available, the success of chemotherapy depends on regular intake of appropriate drugs by the patients. Directly Observed Treatment, Short course chemotherapy (DOTS) is a strategy that is found to be effective and is recommended throughout the world. In India, it is implemented by the Revised National Tuberculosis Control Programme (RNTCP) which was launched in 1997. It involves providing most effective medicine and confirming that it is taken - a health worker ensures that the drug is taken by the patient. Patients are grouped into 3 categories for treatment (Table 41.3).

Resistant tuberculosis If sputum remains positive even after 6 months of treatment, organisms are likely to be resistant. Such patients should be treated with 4-5 drugs, of which 3 are first line drugs and treatment is continued for at least 1 year after the sputum becomes negative. Fluoroquinolones and amikacin may be considered for multidrug resistant strains.

Role of glucocorticoids As steroids depress host defense mechanisms, they should be used only in conditions like tubercular meningitis, miliary tuberculosis, pleural effusion, renal tuberculosis and rapidly progressing pulmonary tuberculosis. Steroids suppress inflammatory reaction which can lead to extensive fibrosis and damage.

Chemoprophylaxis is given only in:

- (i) Contacts of open cases especially children
- (ii) Patients with old inactive disease who have not been adequately treated. INH is used daily (5 mg/kg) for 6-12 months.
- (iii) HIV infected patients exposed to multi drug resistant tuberculosis rifampicin and pyrazinamide are given daily for 2 months.

Table 41.3 : Treatment categories of DOTS chemotherapy in India

Category	Patients	Initial phase daily/ 3 per week	Continuation phase	Total duration (months)
I	• New sputum smear - positive • Sputum negative with extensive pulmonary Tb. • Severe extrapulmonary Tb.	HRZE for 2 m	HR daily for 4 m or HE twice weekly for 6 m	6 8
II	Sputum +ve relapse Sputum +ve failure Sputum +ve interrupted Sputum +ve treatment	HRZES 2 m HRZE 1 m	HRE 5 m	8
III	Sputum negative extrapulmonary	HRZ 2 m	HR 4 m	6

H - INH R = rifampin, Z = pyrazinamide, E = ethambutol, S = streptomycin, m = months

Tuberculosis in AIDS patients Due to depressed immunity, AIDS patients are at a higher risk (25-30 times). AIDS patients are likely to have more severe and rapidly progressing tuberculosis. Adverse effects to anti-tubercular drugs are more common in them. They should be given more vigorous and supervised chemotherapy as the guidelines of DOTS. INH + R + S + Z for 2 months followed by INH + R for 7 months.

Drugs for *Mycobacterium avium* complex (MAC) Infection with MAC is more common and more severe in HIV patients. With the use of prophylactic regimens, the incidence of MAC infections has greatly decreased. In non-HIV patients MAC infection causes milder disease with chronic productive cough. The drugs effective are rifabutin, clarithromycin, azithromycin, fluoroquinolones, ethambutol, clofazimine, amikacin and ethionamide. The macrolides clarithromycin and azithromycin are highly effective - and are the first choice drugs in MAC therapy. Clarithromycin/azithromycin with ethambutol is the preferred regimen (rifabutin may be added) for MAC infection and needs life long treatment. Rifabutin, clarithromycin or azithromycin are used for prophylaxis.

LEPROSY

Leprosy caused by *Mycobacterium leprae* is a chronic infectious disease affecting skin, mucous membranes and nerves. Hansen discovered lepra bacillus in 1873. As lepra bacillus does not grow on artificial media and cannot be transmitted to all animals, it is difficult to culture this organism and study the effect of drugs.

In India leprosy (*kusta roga*) is a major public health problem affecting millions of people.

Drugs Used in Leprosy

- Sulfones: Dapsone
- Rifampicin
- Clofazimine
- Ethionamide and Protionamide

Dapsone

Dapsone is diaminodiphenylsulfone (DDS) and is related to sulfonamides.

Mechanism of action Like sulfonamides, it inhibits the incorporation of PABA into folic acid.

Actions Dapsone is leprostatic. Though it inhibits growth of many other bacteria, the dose needed is high and is therefore not used.

The lepra bacillus develops resistance to dapsone on prolonged use.

Dapsone is completely absorbed on oral administration and reaches high concentrations in skin. It is metabolised in the liver and excreted in bile.

Adverse effects Dapsone is well-tolerated—anorexia, nausea and vomiting are common. Fever, pruritus, rashes and dermatitis can occur. Haemolytic anaemia is the most important dose-related toxicity (more common in patients with G₆PD deficiency). Iron preparations should be given to prevent anaemia. Hepatitis and agranulocytosis are seen. Patients with lepromatous leprosy may develop lepra reactions.

Rifampicin

Rifampicin is rapidly bactericidal to *M. leprae* and is highly effective - a single dose of 1500 mg can kill 99% of the lepra bacilli. It can be conveniently given once monthly. Used in combination with dapsone, it shortens the duration of treatment. Given alone—resistance develops.

Clofazimine

Clofazimine a dye, has weak bactericidal actions against *M. leprae*. It also has anti-inflammatory properties which is useful in

suppressing lepra reactions. It is used orally in multi-drug regimens.

Clofazimine imparts a reddish-black discolouration to the skin specially on the exposed parts which remains for several months. It can also cause dryness of skin, itching and phototoxicity.

Ethionamide

Ethionamide is bactericidal to lepra bacilli but is more expensive and more toxic than dapsone. It can cause gastric irritation, peripheral neuritis and hepatotoxicity. Ethionamide can be used in multidrug regimen in patients who cannot tolerate clofazimine. *Protionamide* is similar to ethionamide.

Other Drugs

Fluoroquinolones Ofloxacin is lepricidal and is suitable for use in multidrug regimens in leprosy along with rifampicin.

Minocycline a tetracycline has been found to have useful activity against *M. leprae* and is being tried in combination regimens to shorten the duration of treatment.

Clarithromycin a macrolide antibiotic has bactericidal activity against *M. leprae*. Given 500 mg daily for 28 days can kill 99% of viable bacilli.

Table 41.4: Multi-drug regimen for leprosy

Drugs	Multibacillary leprosy (for 24 months)	Paucibacillary leprosy (for 6 months)
Rifampicin	600 mg once monthly supervised	600 mg once monthly supervised
Dapsone	100 mg daily self-administered	100 mg daily self-administered
Clofazimine	300 mg once monthly supervised 50 mg daily self-administered	— —
Single-lesion paucibacillary leprosy		
Rifampicin	600 mg	} given as a single dose.
Ofloxacin	400 mg	
Minocycline	100 mg	
All drugs are given orally		

Treatment of Leprosy

For the sake of treatment, leprosy is divided into paucibacillary (non-infectious) and multibacillary (infectious) leprosy. (Table 41.4). Several alternative and short term regimens including drugs like ofloxacin, minocycline and clarithromycin are under evaluation.

WHO has recommended a combination of drugs in leprosy in order to:

1. eliminate persisters
2. prevent drug resistance
3. reduce the duration of therapy.

Lepre reactions are the acute exacerbations that occur in leprosy. They are triggered by acute infections, stress, anxiety and treatment with dapsone.

Type I reactions seen in tuberculoid leprosy are cell mediated, delayed hypersensitivity reactions to the antigens of *M. leprae*. Cutaneous ulcerations occur and existing lesions show more erythema; nerves may be painful and tender. They are treated

with corticosteroids or clofazimine while in mild cases aspirin suffices.

Type II reactions are seen in lepromatous leprosy (are known as *erythema nodosum leprosum* or ENL). New lesions appear and the existing lesions become worse. Fever, lymphadenitis, myositis, and neuralgia may occur. It is a hypersensitivity reaction to the antigens of *M. leprae* - an arthus type reaction.

Type II reactions can be treated with clofazimine which is effective due to its anti-inflammatory properties. Chloroquine, corticosteroids or thalidomide are also effective. Aspirin is effective in mild cases. Dapsone should be continued throughout.

Chemoprophylaxis Only about 1% of contacts develop clinical disease. Dapsone 100 mg daily and rifampicin 600 mg once a month for 6 months or till the contact case becomes noninfectious are recommended for child contacts. Acedapsone is found to be advantageous for chemoprophylaxis as a single IM injection every 10 weeks. All contacts should be examined every 6 months.

Antifungal Drugs

Fungal infections may be systemic or superficial. There has been an increase in the incidence and severity of fungal infections in the recent years. Several unusual and drug-resistant organisms have emerged. This may be consequent to the use of broad spectrum antibiotics, anticancer drugs and HIV infections all of which impair host defense mechanisms. Antifungal drugs may be classified into:

CLASSIFICATION

1. Antifungal antibiotics

Polyene antibiotics -

Amphotericin B, nystatin,
hamycin, natamycin

Others-Griseofulvin

2. Antimetabolites

Flucytosine (5-FC)

3. Azoles

Imidazoles

Clotrimazole, econazole,
miconazole, ketoconazole,
butaconazole, oxiconazole,
sulconazole, isoconazole.

Triazoles

Fluconazole, itraconazole,
terconazole.

4. Miscellaneous

Terbinafine, pneumocandins

5. Other topical agents

Tolnaftate, undecylenic acid,
benzoic acid, salicylic acid,
selenium sulfide, ciclopirox
olamine.

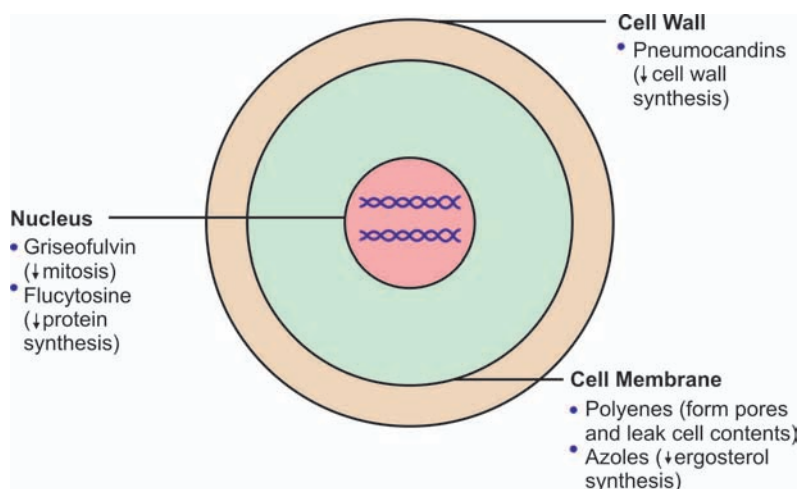


Fig. 42.1 : Sites of action of antifungal drugs

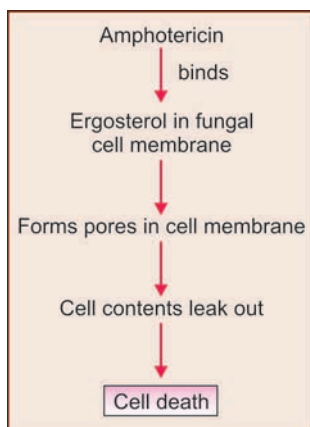
Sites of action Antifungal drugs may act (Fig. 42.1) on the fungal cell wall (pneumocandins), cell membrane (polyenes, azoles) or on the nucleus (griseofulvin, flucytosine).

Antifungal Antibiotics

Amphotericin B obtained from *Streptomyces nodosus* is a polyene antibiotic containing many double bonds.

Antifungal spectrum Amphotericin B has a wide antifungal spectrum. It inhibits the growth of *Candida albicans*, *Histoplasma capsulatum*, *Cryptococcus neoformans*, *Coccidioides*, *Aspergillus* and *Blastomyces dermatitidis*. It is fungistatic at low and fungicidal at high concentrations. Amphotericin B also has activity against *Leishmania*.

Mechanism of Action



Amphotericin B binds to ergosterol present in fungal cell membrane and forms pores in the cell membrane. Through these pores, cell contents leak out resulting in cell death. Since amphotericin has greater affinity for the fungal membrane sterol (ergosterol), action is selective for the fungi.

Pharmacokinetics Amphotericin is not absorbed orally. It is insoluble in water. Given IV, it is widely distributed in the body and has a long $t_{1/2}$ of 15 days.

Adverse effects Fever, chills, muscle spasms, vomiting, dyspnoea, headache and hypotension can be encountered on IV infusion. Amphotericin should be injected slow IV, cautiously - to avoid arrhythmias. Pain and thrombophlebitis at the site of injection are common. Dose should be gradually increased. Renal impairment, neurotoxicity and anaemia due to decreased production of erythropoietin and bone marrow depression can also occur. Concurrent administration of other nephrotoxic drugs should be avoided.

Uses

- Amphotericin B is the drug of choice for all life-threatening mycotic infections. 0.5 mg/Kg in 5% dextrose infused over 4 hours is the usual therapeutic dose. Amphotericin B is given intravenously in the treatment of mucormycosis, invasive aspergillosis, cryptococcosis, sporotrichosis, trichosporanosis, blastomycosis, histoplasmosis, coccidioidomycosis and paracoccidioidomycosis.
- In cystitis due to candida, amphotericin B is used to irrigate the bladder.
- Amphotericin B is also used to prevent relapse of cryptococcosis and histoplasmosis in patients with AIDS.
- Amphotericin B can be given orally in fungal infections of the gut.
- It is used topically in candidiasis (3% lotion, cream, ointment).
- Leishmaniasis: In kala-azar and mucocutaneous leishmaniasis, amphotericin is used as an alternative.

Nystatin obtained from *Streptomyces noursei* has actions similar to amphotericin B. But as it is too toxic for systemic use, it is used topically. It is used for local candidial infections like oral thrush and vaginal candidiasis. 5 ml oral nystatin suspension should be swished in the mouth and then

swallowed 4 times a day to treat the candida in the esophagus.

Hamycin is similar to nystatin. It is used topically for cutaneous candidiasis and otomycosis.

Griseofulvin is a fungistatic derived from *Penicillium griseofulvum*. It is effective in superficial dermatophytosis (caused by *Trichophyton*, *Microsporum* and *Epidermophyton*). Griseofulvin is the antifungal given orally for superficial dermatophytosis.

Mechanism of action Griseofulvin binds to microtubular protein in the nucleus, disrupts the mitotic spindle and inhibits mitosis in the fungus. It gets deposited in the newly forming skin, binds to keratin and protects the skin from getting newly infected.

Pharmacokinetics Griseofulvin is poorly water soluble with poor bioavailability. Absorption can be enhanced by using microfined drug particles and by giving it with fatty food. Griseofulvin is a microsomal enzyme inducer. **Adverse effects** include allergic reactions, hepatitis and neurotoxicity.

Drug Interactions

- Phenobarbitone reduces the absorption of griseofulvin - may result in therapeutic failure
- Griseofulvin enhances warfarin metabolism by inducing microsomal enzymes.
- Alcohol should be avoided because griseofulvin can cause intolerance to alcohol.

Uses

Griseofulvin is used orally in superficial dermatophytosis. Dose : 1 g daily. It is particularly preferred when a larger area is involved when topical antifungals are not

suitable. Duration of treatment varies from 3 weeks to 1 year depending on the site of infection. Nail infections require 6-12 months of treatment.

Antimetabolites

Flucytosine is a fluorinated pyrimidine effective against *Cryptococcus neoformans* and some strains of *Candida*. It is taken up by the fungal cells and converted to 5-fluorouracil which inhibits DNA synthesis.

Bone marrow depression and gastrointestinal disturbances are the most common adverse effects. It is used with amphotericin B (used alone, resistance develops rapidly) in cryptococcal meningitis and systemic candidiasis.

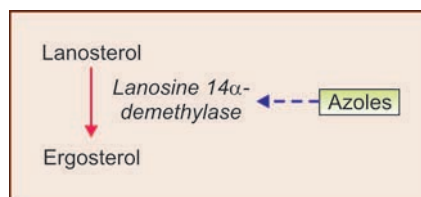
Azoles

Imidazoles and Triazoles

The older antifungals need to be given intravenously and are quite toxic. Azoles are newer synthetic antifungals that are effective orally and are less toxic. Imidazoles and triazoles are azoles; the triazoles have more selective effect on fungal sterol synthesis than imidazoles. Triazoles are also longer acting.

Antifungal spectrum Azoles have a broad spectrum antifungal activity. They inhibit dermatophytes, candida, *Cryptococcus neoformans*, *H.capsulatum* and other deep mycoses.

Mechanism of Action



Azoles inhibit the synthesis of ergosterol, an important component of the fungal cell membrane. Azoles inhibit the fungal

cytochrome P450 enzyme lanosterol 14 α -demethylase which catalyses the conversion of lanosterol to ergosterol. Thus it results in ergosterol deficiency which alters the enzyme activity and fungal replication. They also interfere with the function of some fungal enzymes and inhibit the growth of the fungi.

Of the azoles, clotrimazole and miconazole are used only topically.

Ketoconazole (KTZ) is the first oral azole to be available. It is well-absorbed from the gut. Food and low gastric pH enhance absorption.

Adverse reactions include gastric irritation, nausea, vomiting, headache, allergic reactions, and rarely fatal hepatotoxicity. In large doses KTZ inhibits the biosynthesis of adrenal and gonadal steroids in humans—resulting in gynaecomastia, infertility, decreased libido, azoospermia, menstrual irregularities and hypertension.

Preparations FUNGICIDE, NIZRAL—ointment, shampoo, 20 mg tablets are available.

Drug Interactions

- Antacids, H₂ receptor blockers, and proton pump inhibitors reduce the bioavailability of KTZ because acidic medium is necessary for KTZ dissolution.
- Rifampicin and phenytoin induce KTZ metabolism and decrease its efficacy.

Uses (Table 42.1)

- Mucocutaneous candidiasis and dermatophytosis can be treated with ketoconazole.
- It is also useful in Cushing's syndrome.
- Though KTZ is useful in deep mycoses, it is not preferred in them because of slow response, toxicity and long duration of treatment (6 to 12 months) required.

Table 42.1: Drugs used in fungal infections

<i>Fungal infection</i>	<i>Drug of Choice</i>	<i>Alternative Drugs</i>
<i>Systemic</i>		
Invasive aspergillosis	Amphotericin	Itraconazole
Blastomycosis	Amphotericin	Itraconazole Ketoconazole
Candidiasis	Fluconazole	Amphotericin Flucytosine Ketoconazole
Coccidioidomycosis	Amphotericin Itraconazole Fluconazole	
Cryptococcosis	Amphotericin + Flucytosine Fluconazole	Itraconazole
Histoplasmosis	Amphotericin Itraconazole	Fluconazole
Mucormycosis	Amphotericin Flucytosine	Itraconazole
Paracoccidioidomycosis	Fluconazole Itraconazole	Amphotericin
Sporotrichosis	Amphotericin	Itraconazole

Clotrimazole and *miconazole* are used topically in dermatophytic infections (ringworm) and mucocutaneous candidiasis (Table 42.2). *Miconazole* penetrates the cutaneous layer - stratum corneum and remains at this site for 3-4 days. It has better efficacy than *clotrimazole*. *Clotrimazole* troche is available for oral thrush. Both can cause mild irritation at the site of application - particularly on mucous membrane. Skin preparations can rarely cause rashes, oedema and pruritus.

Preparations

- *Clotrimazole* (CANDID, CLODERM)
Lotion, cream, vaginal pessary 100 mg inserted into the vagina at bed time for 7 days or 200 mg daily for 3 days or 500 mg single dose.
- *Miconazole* (DAKTARIN, ZOLE) 2-4% ointment, gel, cream, lotion and vaginal suppository (100, 200 mg).

Fluconazole is water soluble, well-absorbed orally and attains good CSF concentration. Hence it is useful even in fungal meningitis. *Fluconazole* is available for oral and IV use. *Adverse effects* are mild gastrointestinal disturbances, headache and rashes. Since it

has very little effect on hepatic microsomal enzymes, drug interactions are less common.

Uses

Fluconazole is used in cryptococcal meningitis after initial treatment with amphotericin B and is the drug of choice in coccidioidal meningitis. It is also useful in systemic candidiasis and other systemic fungal infections. Though it is also effective in tinea infections and mucocutaneous candidiasis, its higher cost makes it less preferable.

Itraconazole is the most potent azole. Given orally, its absorption is increased by food and gastric acid. Its effect on hepatic microsomal enzyme inhibition is less; does not affect steroid synthesis. Thus it is preferred over *ketoconazole*. It has a $t_{1/2}$ of 36 hours. It is available both for oral and IV use. Adverse effects include headache, dizziness, GI disturbances and allergic reactions. It can rarely cause hepatitis and hypokalemia.

Itraconazole is the drug of choice in most systemic mycoses (without meningitis) 100 mg BD with food. It can be given IV in severe infections.

It can also be used in onychomycosis, candidiasis and dermatophytoses but is expensive. (ITASPOR, SPORANOX 100 mg cap).

Econazole, *terconazole*, *tioconazole*, *butaconazole*, *oxiconazole* and *sulconazole* are all azoles available for topical use as creams and lotions for use in dermatophytoses and mucocutaneous candidiasis.

Terbinafine is a synthetic antifungal that is effective against dermatophytes and *Candida*. It is orally effective and is fungicidal. It gets concentrated in the keratin like griseofulvin. It inhibits an enzyme needed for biosynthesis of ergosterol by fungi.

Table 42.2: Drugs used in superficial mycosis

	Topical	Oral
Ringworm	An azole	Terbinafine Itraconazole
Candidiasis		
• Cutaneous	Amphotericin An azole Ciclopirox Nystatin	
• Oropharyngeal	Amphotericin An azole Nystatin Fluconazole	Itraconazole
• Vaginal	An azole Nystatin	Fluconazole

Adverse effects are rare – gastrointestinal disturbances, rashes and headache can occur. Terbinafine is used in dermatophytosis, pityriasis, onychomycosis and candidiasis. It is particularly preferred in onychomycosis - 250 mg OD for 12 weeks - where it is superior to azoles and griseofulvin.

Dose 250 mg once daily; (SEBIFIN) 1% cream is also available.

Pneumocandins or Echinocandins

Pneumocandins inhibit the formation of the fungal cell wall. They inhibit the synthesis of an important component of the fungal cell wall - a glucose polymer as a result of which the fungal cell lysis occurs.

Echinocandins include caspofungin, micafungin and amorolfine. *Caspofungin* has activity in candidiasis, aspergillosis and in *Pneumocystis carinii* infections. *Micofungin* is effective against candida and aspergillus while *amorolfine* is useful in fungal infections of the nail.

Other Topical Antifungal Agents

Apart from nystatin, clotrimazole, miconazole and terbinafine, some drugs like salicylic acid, benzoic acid, tolnaftate and cyclopirox olamine are used topically for dermatophytosis and pityriasis versicolor.

Selenium sulfide is useful in tinea versicolor caused by *Malassezia furfur*, and also in dandruff. SELSUN is 2.5% suspension of selenium sulfide in a shampoo base. It is irritant to the eyes and the odour is unpleasant.

43

Antiviral Drugs

Viruses are intracellular parasites and depend on the host cells for their food, growth and multiplication. The virus attaches itself to the host cell membrane and penetrates it (entry), DNA/RNA is released in the host cell (uncoating) where it is duplicated. The viral components are assembled (assembly) and the mature viral particle is then released from the host cell (budding and release). Chemotherapy can interfere with any of these steps (Table 43.1). But drugs that interfere with viral replication may also interfere with host cell function. Currently, efforts are being made to develop drugs that selectively inhibit the virus without affecting the host cell function.

There are two types of viruses- DNA and RNA viruses and there are minor differences in their replicative cycles. The DNA virus depends on host cell enzymes (mRNA polymerase) to synthesize mRNA while RNA viruses use their own enzymes for mRNA synthesis.

Retroviruses—a type of RNA viruses are known to cause AIDS. In retroviruses a viral enzyme reverse transcriptase is involved in replication. Two groups of antiviral drugs inhibit this enzyme. The immature virion formed undergoes maturation with the help of the enzyme protease. Inhibitors of this enzyme protease prevent maturation of the virions.

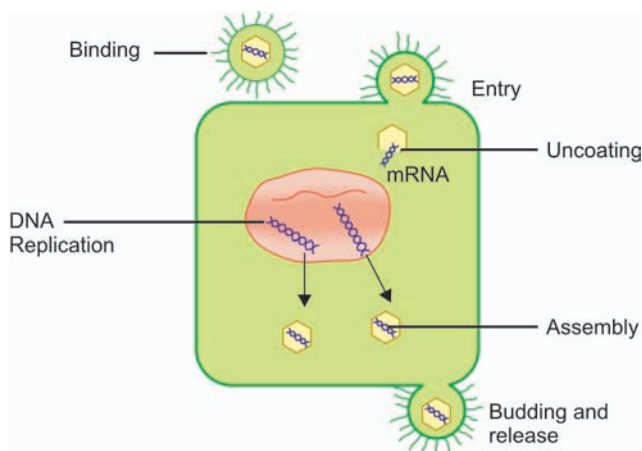


Fig. 43.1: Sites of action of antiviral drugs
Antiviral drugs may act on any of the stages of viral replication

Antiviral drugs may be classified as follows

CLASSIFICATION

1. *Anti-herpes virus agents*

Acyclovir, ganciclovir, famciclovir, penciclovir, valaciclovir, idoxuridine, trifluridine, vidarabine, foscarnet, fomivirsen, cidofovir

2. *Anti-influenza virus agents*

Amantadine, rimantadine, oseltamivir, zanamivir,

3. *Others*

Ribavirin, interferons, lamivudine.

4. *Anti-retroviral agents*

- *Nucleoside Reverse Transcriptase inhibitors (NRTI)*

Zidovudine, didanosine, stavudine, zalcitabine, lamivudine, abacavir

- *Nonnuclease Reverse Transcriptase inhibitors (NNRTI)*

Nevirapine, efavirenz, delavirdine

- *Protease inhibitors (PI)*

Saquinavir, indinavir, ritonavir, nelfinavir, amprenavir, lopinavir

- *Nucleotide reverse transcriptase inhibitors. (NTRTI), Tenofovir*

ANTI-HERPES VIRUS AGENTS

Acyclovir is effective against Herpes simplex virus (HSV) type 1 and type 2, Varicella zoster virus (VZV) and Epstein-Barr virus (EBV).

Mechanism of action Acyclovir (Fig. 43.2) is taken up by the virus infected cell, converted to acyclovir triphosphate and this inhibits viral DNA synthesis by inhibiting viral DNA polymerases and causing DNA chain termination.

Oral absorption of acyclovir is poor; it is well distributed—attains good concentration in the CSF and aqueous humour.

Adverse effects Acyclovir is well-tolerated; nausea, diarrhoea, headache and rashes may

occur occasionally. Topical acyclovir can cause burning and irritation. Given IV, it may cause renal and neurotoxicity but are uncommon.

Uses

1. *HSV infections* Infection with HSV-1 causes diseases of the mouth, face, skin, oesophagus or brain. HSV-2 usually causes infections of the genitals, rectum, skin, hands or meninges (Table 43.2).

- Oral acyclovir is effective in primary and recurrent genital and labial herpes. In mild cases, topical acyclovir can be tried. In recurring genital herpes—oral acyclovir is given for 1 year.
- *HSV encephalitis* and other severe HSV infections—IV acyclovir is the drug of choice.
- *HSV keratoconjunctivitis* Acyclovir eye drops are effective.

2. *Herpes zoster* Acyclovir shortens the duration of illness. In immunodeficient patients—IV acyclovir is used.

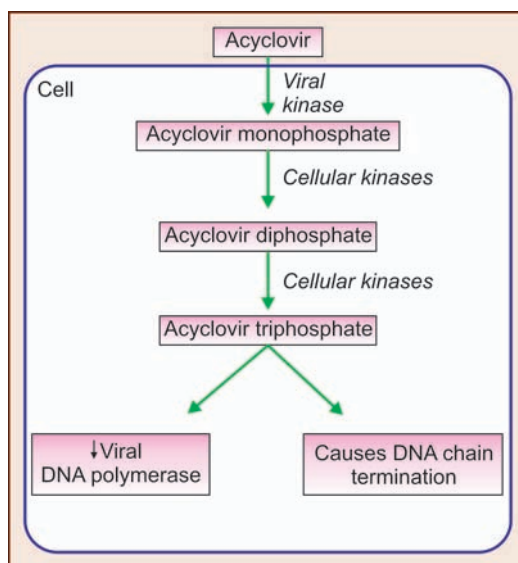


Fig. 43.2: Mechanism of action of acyclovir

3. *Chickenpox* In adults and in immunodeficient patients, acyclovir reduces duration and severity of illness. In children, routine use is not recommended.

Valacyclovir is a prodrug of acyclovir. *Famciclovir* is a prodrug of penciclovir—used in HSV and VZV infections.

Ganciclovir is effective against herpes viruses especially Cytomegalovirus (CMV). Toxicity includes myelosuppression and gonadal toxicity. It is used in immunocompromised patients with CMV retinitis.

Idoxuridine is effective in DNA viruses. It acts by inhibiting viral DNA synthesis. Idoxuridin is used topically in HSV keratitis (it is too toxic for systemic use). Eyelid edema, itching, allergic reactions may occur.

Trifluridine is used topically in HSV eye infections.

Foscarnet is given intravenously to treat CMV retinitis as an alternative to ganciclovir.

Vidarabine was used earlier for HSV and VZV infections but is now replaced by acyclovir.

Fomivirsen is effective against cytomegalovirus. It is given by intravitreal injection in severe cases of CMV retinitis which do not respond to other drugs.

Cidofovir is a cytidine analog effective against herpes viruses, VZV, CMV, EBV, Human papilloma virus (HPV) and adenoviruses – has a broad spectrum of activity. Cidofovir acts by inhibiting viral DNA synthesis. It is

given intravenously to prevent the progression of CMV retinitis in AIDS patients. It can also be used topically in HPV skin infections.

ANTI-INFLUENZA VIRUS AGENTS

Amantadine and **Rimantadine** inhibit the replication of influenza A viruses. They are generally well-tolerated; nausea, vomiting, diarrhoea, dizziness, insomnia and ankle oedema are reported. Rimantadine is longer-acting and has fewer adverse effects.

Uses (Table 43.2)

1. Treatment of influenza A during an epidemic- they reduce the duration and severity; dose: 200 mg/day for 5 days.
2. Prophylaxis of influenza A during an epidemic especially in high-risk patients. Also for seasonal prophylaxis in high-risk patients.
3. Parkinsonism—amantadine enhances the release of dopamine and is beneficial in parkinsonism.

Oseltamivir and **Zanamivir**—inhibit viral replication. They act by inhibiting the neuraminidase activity which is essential for the release of daughter virions. Oseltamivir is given orally, can cause nausea and vomiting while zanamivir is given by inhalation which can occasionally cause respiratory distress.

Table 43.1: Drugs acting on viral replication steps

<i>Viral replication steps</i>	<i>Drugs effective</i>
Uncoating	Amantadine, Rimantadine
Transcription	Interferons
Translation of viral proteins	Fomivirsen, interferons
DNA and RNA replication	Acyclovir, cidofovir, famciclovir, ganciclovir, foscarnet, idoxuridin, ribavirin, sorivudine
Assembly	Interferons
Budding and release	Zanamivir, oseltamivir

Oseltamivir and zanamivir are indicated in the prevention and treatment of influenza.

Docosanol suppresses viral replication by inhibiting the viral entry into the cell. It is used topically in the treatment of orolabial herpes. It should be used early at the onset of lesion.

OTHER ANTIVIRAL AGENTS

Ribavirin has broad spectrum antiviral activity. It is effective against influenza A and B, respiratory syncytial virus (RSV) and many DNA and RNA viruses. It is used as an aerosol in RSV bronchiolitis in children. Also it can be used in severe influenza and measles in immunocompromised patients.

Interferons are cytokines produced by host cells in response to viral infections. There are three types - α , β and γ interferons in man. They also have immunomodulating and antiproliferative properties. They inhibit the multiplication of many DNA and RNA viruses.

Adverse effects include myelosuppression, hypotension, arrhythmias, alopecia, headache and arthralgia. It can also cause neurotoxicity resulting in confusion, sedation and rarely seizures.

Uses

1. Chronic hepatitis B and C.
2. Kaposi's sarcoma in AIDS patients.
3. Genital warts caused by Papilloma virus—interferons are injected into the lesion.
4. Hairy cell leukaemia.
5. HSV, herpes zoster and CMV infections in immunocompromised patients.
6. Rhinovirus cold—interferon α is given intranasally for prophylaxis.

ANTI-RETROVIRAL DRUGS

Acquired immunodeficiency syndrome (AIDS) results from infection with Human immunodeficiency virus (HIV) - a retrovirus. The spread of HIV infection is alarmingly high with around 20 million deaths reported.

Table 43.2: Routes of administration and indications of some antiviral drugs

Drugs	Routes	Indications
Acyclovir	Topical Oral IV	Herpes genitalis, HSV eye infections Herpes genitalis, mucocutaneous HSV, chickenpox HSV encephalitis, severe herpes genitalis, chickenpox/herpes zoster in immunocompromised patients
Idoxuridine } Trifluridine }	Topical	HSV keratitis
Ganciclovir	IV/oral	CMV infections
Foscarnet	IV	CMV retinitis, acyclovir resistant HSV infections
Amantadine } Rimantadine }	Oral	Influenza A
Ribavirin	Aerosol oral/IV	RSV bronchiolitis Severe influenza and measles
Interferon α	IV	Chronic hepatitis B and C, genital warts, Kaposi's sarcoma

Two types of HIV have been identified - HIV-1 and HIV-2.

Drugs used in the treatment of AIDS are of two groups - the reverse transcriptase inhibitors and protease inhibitors. A combination of drugs is used in AIDS to improve prognosis - known as Highly Active Antiretroviral Therapy (HAART). A HAART regimen includes two NRT inhibitors with either NNRT or protease inhibitors. Using a HAART regimen suppresses HIV replication, plasma HIV RNA levels are greatly reduced and prolongs patient survival. HAART also has some disadvantages of being difficult to follow and is associated with adverse effects from drugs and with relapse.

HIV has a high mutation rate and therefore easily develops resistance to the drugs. Multi-drug resistant strains have emerged and they further complicate treatment.

Table 43.3: Adverse effects of nucleoside reverse transcriptase inhibitors

Drug	Adverse effects
Zidovudine	Myelosuppression headache, nausea, insomnia
Didanosine	Pancreatitis, peripheral neuropathy, diarrhoea, hyperuricaemia
Stavudine	Peripheral neuropathy, stomatitis
Zalcitabine	Peripheral neuropathy, stomatitis, pancreatitis
Lamivudine	Headache, nausea
Abacavir	Hypersensitivity syndrome

Nucleoside Reverse Transcriptase Inhibitors (NRTI)

Zidovudine is the first drug to be used in the treatment of HIV infection. Others including didanosine, stavudine, zalcitabine, lamivudine and abacavir were developed later.

Mechanism of action NRT inhibitors are converted to their corresponding triphosphate derivatives which have a high affinity for reverse transcriptase, an enzyme specific to HIV and required for DNA synthesis. The NRT inhibitors are nucleoside analogs. They competitively inhibit reverse transcriptase and terminate DNA chain elongation.

Pharmacokinetics The NRT inhibitors are well absorbed when given orally. Their plasma $t_{1/2}$ varies from 1–4 hours. All NRT inhibitors (except abacavir) are excreted in the urine.

Zidovudine (Azidothymidine, AZT) is a thymidine analog, active against HIV infections and other retroviruses.

Adverse effects Bone marrow suppression is the most prominent adverse effect (Table 43.3) of zido-vudine. It is more common in patients with advanced AIDS. Anaemia can be treated with erythropoietin while neutropenia needs G-CSF or GM-CSF. Headache, nausea, myalgia, fatigue and insomnia can occur. High doses cause myopathy and neurotoxicity.

Uses

AZT is the drug of choice in AIDS. Treatment with AZT results in prolonged survival, decreased opportunistic infections, weight gain and in early cases it delays disease progression.

Given during pregnancy and continued in new borns for 6 weeks, AZT reduces the risk

of transmission to the baby. But it has **no** prophylactic value in those who are accidentally exposed to HIV infection (e.g. following blood transfusion). Combination therapy of AZT with other antiretroviral drugs gives better results.

Didanosine, Zalcitabine, Stavudine Lamivudine and Abacavir are other reverse transcriptase inhibitors effective against AZT resistant HIV infections. They are used as alternatives to AZT or with AZT in patients with advanced HIV who are intolerant to AZT or are not responding to AZT.

Lamivudine is well tolerated with no significant adverse effects in therapeutic doses other than headache and nausea: Abacavir can cause a hypersensitivity syndrome with fever, rash and bronchitis which can be fatal. Hence abacavir should be withdrawn at the onset of such symptoms. Peripheral neuropathy, pancreatitis, rash, fever and headache can occur with didanosine, stavudine and zalcitabine.

Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)

The NNRT inhibitors nevirapine, delavirdine and efavirenz are synthetic compounds.

Mechanism of action – The NNRT inhibitors bind to reverse transcriptase (are not converted to triphosphate derivatives) and bring about a change in the enzyme thereby inactivating the enzyme. NNRT inhibitors are effective only against HIV -1(not against HIV-2 and other retroviruses)

Adverse effects Allergic reactions ranging from skin rashes, pruritus to Stevens Johnson syndrome and toxic epidermal necrolysis can occur. Other effects include headache, dizziness, drowsiness, nightmares, confusion, vomiting, diarrhoea and skin rashes. Efavirenz has teratogenic effects in monkeys

and is contraindicated in pregnant women. Nevirapine can occasionally cause fulminant hepatitis.

Uses

NNRTIs are used in the treatment of HIV infections in combination with other drugs. Nevirapine can be tried in pregnant women during labour and in newborn to prevent vertical transmission to the newborn.

Protease Inhibitors (PI)

Saquinavir is the first agent in this group to be used.

Mechanism of action HIV protease activity is essential for the activation of viral enzymes and HIV replication. It is needed for the production of mature virion and for viral infectivity. The protease inhibitors bind competitively to HIV protease and block viral maturation. This makes the daughter viral particles immature and noninfectious.

Pharmacokinetics–Saquinavir has poor oral bioavailability (4-10%) while others are well absorbed. All PIs are extensively bound to plasma proteins. They are all metabolised by hepatic microsomal enzymes and are also

NNRT inhibitors

- Nevirapine, delavirdine, efavirenz.
- Bind reverse transcriptase of HIV – 1 and inactivate it.
- Given orally, they are well absorbed and extensively bound to plasma proteins.
- Metabolised by microsomal enzymes. Nevirapine and efavirenz are enzyme inducers; delavirdine is an enzyme inhibitor – drug interactions are common.
- Used in HIV–1 infections in combination with other antiretroviral drugs.

Protease inhibitors

- Bind HIV protease and prevent viral maturation
- All except saquinavir all well absorbed
- All are metabolised by microsomal enzymes and inhibit these enzymes – drug interactions are common.
- Gastrointestinal disturbances are the common side effects
- Used in combination with other antiretroviral drugs in HIV infections.

microsomal enzyme inhibitors. Hence many drug interactions can occur.

Adverse effects—Protease inhibitors are well tolerated. Gastrointestinal symptoms like nausea, vomiting and diarrhoea can occur. For other adverse effects see Table 43.4.

Table 43.4: Adverse effects of protease inhibitors

Drug	Adverse effects
Saquinavir Ritonavir	Gastrointestinal disturbances, Gastrointestinal disturbances, taste perversion, perioral and peripheral paresthesias, ↑ Serum cholesterol, ↑TG
Indinavir	Crystalluria, nephrolithiasis (advise lot of fluid intake) ↑serum bilirubin, alopecia, dry skin, gastrointestinal disturbances
Nelfinavir	Diarrhoea ↑ Blood glucose ↑ Serum lipids
Amprenavir	Gastrointestinal disturbances, rash, ↑ blood glucose, avoid high ↓ fat meals
Lopinavir	Gastrointestinal disturbances ↑ Serum lipids

Uses

Protease inhibitors are used in combination with other antiretroviral drugs in the treatment of HIV infections. Ritonavir inhibits microsomal enzymes and thereby prolongs the plasma half-life of other protease inhibitors. This beneficial drug interaction, permits the use of lower doses of other PIs with ritonavir.

Other Drugs

Enfuvirtide is a recent introduction for use in AIDS. It inhibits the binding of the virus to the host cell membrane and thereby blocks the entry of the virus. It is tried as an add-on drug in patients not responding to other antiretroviral drugs in HIV-1 infected patients.

Many new antiretroviral agents are under evaluation.

Drug interactions of antiretroviral drugs

- Since AZT causes myelosuppression, it should not be combined with other myelosuppressants.
- Plasma levels of abacavir are increased by alcohol.
- Nevirapine and efavirenz are microsomal enzyme inducers— concurrent administration of rifampicin and ketoconazole should be avoided. Oral contraceptives can fail, hence alternative methods of contraception should be followed.
- Delavirdine is a microsomal enzyme inhibitor.

Chemotherapy of Malaria

Malaria is caused by protozoa of the genus *Plasmodium*, transmitted through the bite of a female *Anopheles* mosquito. It is a major public health problem in most of the developing countries including India. Every year about 200-500 million cases of malaria occur throughout the world with about 2 million deaths.

Life cycle of the malaria parasite. The bite of an infected female *Anopheles* mosquito introduces sporozoites into the blood stream of man (Fig 44.1). These sporozoites enter the liver cells where they develop and multiply and the cells rupture to release merozoites (pre-erythrocytic stage). The merozoites enter red blood cells to develop and mature (erythrocytic stage/erythrocytic schizogony) and the RBCs rupture releasing merozoites which invade fresh RBCs and continue to multiply. The rupture of RBCs releases the products of the parasite which induce chills and fever. In *P. vivax* and *P. ovale* species, some sporozoites in the liver cells enter a dormant stage (hypnozoites or sleeping forms) which can multiply later (even after several months) resulting in relapse (exoerythrocytic stage). Some merozoites entering the RBCs, differentiate into male and female sexual forms or gametocytes. These forms enter the mosquito when they suck the blood and undergo sexual cycle in the mosquito.

The 4 species of the malarial parasite include:

- *P. falciparum*—causes most severe form of malaria (malignant tertian) which can be fatal. But relapses do not occur because it has no exoerythrocytic stage in its life cycle.
- *P. vivax* causes less severe malaria (benign tertian) with a low mortality rate. Relapses can occur because of the exoerythrocytic forms or hypnozoites.
- *P. ovale* is mostly seen in Africa, causes milder type similar to *P. vivax* - but relapses can occur.
- *P. malariae* is also of milder type similar to *P. vivax* (benign quartan) with no exoerythrocytic cycle.

Chemical Classification

4-aminoquinolines

Chloroquine, amodiaquine

8 – aminoquinolines

Primaquine, bulaquine

Quinoline methanols

Quinine, quinidine, mefloquine

Acridine

Mepacrine

Folate antagonists

Proguanil, sulfadoxine, pyrimethamine

Phenanthrene methanol

Halofantrine, atovaquone

Sesquiterpine lactones

Artesunate, artemether, arteether

Therapeutic Classification

- | | |
|---|--|
| 1. <i>Causal Prophylactics</i> (primary tissue schizontocides) –
(destroy parasite in liver cells and prevent invasion of erythrocytes) | Primaquine, pyrimethamine |
| 2. <i>Blood schizontocides</i> (suppressives)
(destroy parasites in the RBCs and terminate clinical attacks of malaria.) | Chloroquine, quinine, mefloquine, halofantrine, pyrimethamine, chloroguanide, artemisinin. |
| 3. <i>Tissue schizontocides used to prevent relapse</i> (hypnozoitocidal drugs) –
(act on hypnozoites of <i>P. vivax</i> and <i>P. ovale</i> that produce relapses). | Primaquine |
| Radical curatives-
(Eradicate <i>P. vivax</i> and <i>P. ovale</i>) | Blood schizontocides+ hypnozoitocidal drugs |
| 4. <i>Gametocidal drugs</i>
(destroy gametocytes and prevent transmission). | Primaquine, chloroquine, quinine. |

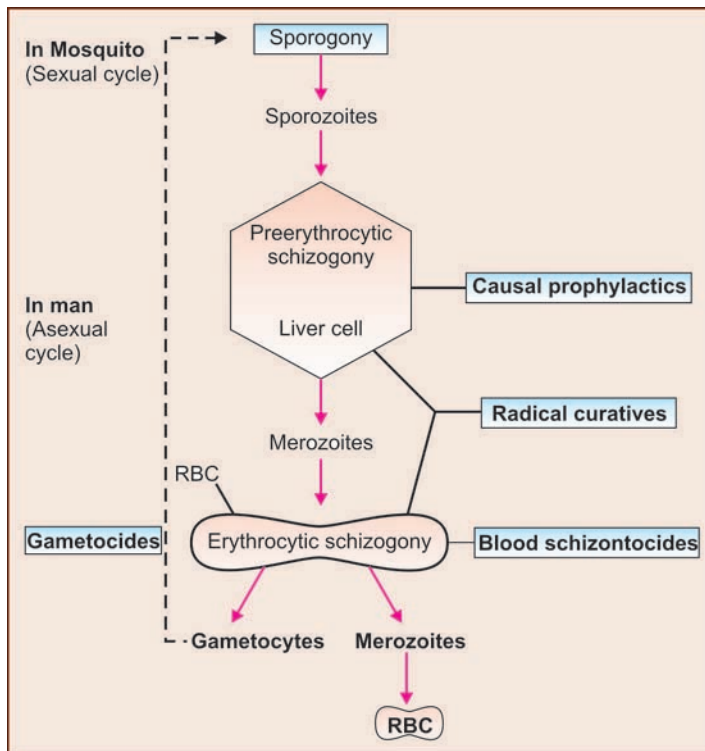
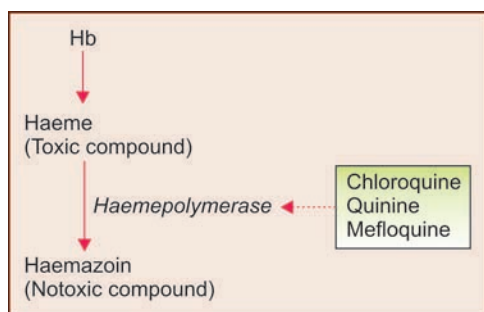


Fig 44.1: Stages of life cycle of the malaria parasite and drugs acting on these stages

Chloroquine

Chloroquine is a synthetic 4-aminoquinoline. **Antimalarial actions** Chloroquine is a highly effective blood schizonticide with activity against all 4 species of plasmodia. It completely cures falciparum malaria. It is rapidly acting - patients become afebrile in 24-48 hr. Chloroquine also destroys gametocytes of *P. vivax*, *P. ovale* and *P. malariae*. Chloroquine is safe in pregnancy. It also has anti-inflammatory properties and is used in rheumatoid arthritis as a disease-modifying antirheumatic drug. It has activity against *Giardia lamblia* and *Entamoeba histolytica*.

Mechanism of action is not clear. Chloroquine is a base. It concentrates in acidic food vacuoles of the parasite. Malarial parasites digest the host haemoglobin and transport it into their acidic food vacuoles (which is their source of aminoacids). In this process a toxic product 'haeme' is formed.



This haeme is converted to nontoxic 'haemazoin' a malarial pigment, by the enzyme haeme polymerase. Chloroquine, quinine and mefloquine inhibit the enzyme haemepolymerase resulting in accumulation of haeme which causes lysis of the parasite membrane and thereby death of the parasite. Chloroquine also prevents the digestion of haemoglobin by the parasite thereby depriving the parasite's aminoacid supply.

Chloroquine resistant strains of *P. falciparum* are now common throughout the world. Chloroquine is rapidly transported out of the food vacuole by the resistant strains. Chloroquine resistant *P. vivax* strains are also increasing and posing a problem in controlling malaria. Several studies have shown that resistance to chloroquine can be reversed by using drugs like verapamil, chlorpheniramine and desipramine. But the benefits of their clinical application need to be established.

Pharmacokinetics Chloroquine is rapidly and well absorbed from the gut. It has a high affinity for melanin rich tissues and nuclear chromatin. It is metabolized by hepatic microsomal enzymes and is largely excreted in the urine.

Adverse effects Doses used for the treatment of malaria are often poorly tolerated as compared to prophylactic doses. Nausea and vomiting may be quite severe. Prior treatment with an antiemetic 30 minutes before chloroquine is generally practiced. Pruritus, headache, visual disturbances, insomnia and skin rashes may occur. IV chloroquine may cause hypotension, widening of QRS complex and arrhythmias. High doses can also cause cardiomyopathy, peripheral neuropathy and psychiatric problems. Long-term suppressive therapy can cause blurring of vision, confusion, bleaching of hair and rarely blood dyscrasias. Prolonged treatment with high doses can cause irreversible retinopathy.

Uses (Table 44.1)

1. **Malaria** Chloroquine is highly effective in the treatment of malaria due to sensitive strains of all 4 species - Chloroquine phosphate 250 mg tab (contains 150 mg base) Dose 600 mg (base) stat, 300 mg after 6 hours and 300 mg for the next 2 days. It is also used for the prophylaxis- 300 mg base per week.

- | | |
|--|--|
| 2. Extraintestinal amoebiasis (Page 321) | } Effective because of anti inflammatory property. |
| 3. Rheumatoid arthritis | |
| 4. Photogenic reactions | |
| 5. Lepra reactions (Page 298) | |

Precautions and Contraindications

- Chloroquine should be avoided or used carefully in patients with myopathy and hepatic, gastrointestinal or neurological disorders.
- Concurrent use of gold or d-penicillamine with chloroquine can cause more severe dermatitis.
- Chloroquine, quinine and mefloquine should not be given concurrently because they compete for accumulation in the parasite and may result in therapeutic failure. Also, chloroquine + mefloquine → increased risk of seizures.
- Chloroquine + halofantrine → increased risk of arrhythmias. Hence a gap of at least 12 hours should be given if patients have to be switched over from chloroquine to quinine/mefloquine/halofantrine.
- Chloroquine should be avoided in patients with retinal diseases. When chloroquine is given in high doses for a long time, regular neurological and eye examination should be done.

Quinine

Quinine is an alkaloid obtained from the bark of the cinchona tree. It destroys erythrocytic forms of the parasite similar to chloroquine and is useful as a suppressive. It is also gametocidal for three species of the malarial parasite except for *P. falciparum*. Mechanism of action is unknown. It may act like chloroquine by inhibiting the enzyme haeme polymerase.

Other Actions

- Quinine also has mild analgesic and antipyretic activity.
- Like quinidine it is also a myocardiac depressant. IV administration can cause significant hypotension.
- It acts as local anaesthetic and has skeletal muscle relaxant properties.
- Quinine stimulates the uterus and is an abortifacient.

Pharmacokinetics Quinine is well absorbed orally, widely distributed in the body, metabolized in the liver and excreted in the urine.

Adverse Effects are high

- Quinine is highly bitter and is a gastric irritant-causes nausea, vomiting and epigastric pain-hence poorly tolerated.
- Hypoglycaemia can be quite profound to result in coma. Hypoglycaemia may be because - i. quinine stimulates the insulin release. ii. parasite consumes glucose.
- Cinchonism with ringing in the ears, headache, nausea, visual disturbances and vertigo may be encountered.
- In more severe poisoning, hypoglycaemia, fever, delirium, confusion, hypotension, cardiac arrhythmias and coma may develop. Death is due to respiratory arrest.
- Black water fever - quinine can precipitate acute haemolytic anaemia with renal failure, haemoglobinuria and fever, which can be fatal. Fortunately this complication is uncommon.

Uses

- Quinine is used in the treatment of resistant falciparum malaria and cerebral malaria. Dose - Table 44.1.
- Nocturnal muscle cramps.

Mefloquine

Mefloquine in a single dose is highly effective against erythrocytic forms of the malaria parasite including– the multi-drug resistant (MDR) strains of *P. falciparum*.

Mefloquine gets concentrated in the acidic vacuoles of the parasite. Mechanism of action is not exactly known but it is thought to act like chloroquine by inhibiting haeme polymerase in the parasite. Some strains of *P. falciparum* have developed resistance to mefloquine in parts of Asia.

It is well absorbed orally and has a long $t_{1/2}$ of nearly 20-30 days—as it undergoes extensive enterohepatic circulation.

Nausea, vomiting, dizziness, confusion, abdominal pain and bradycardia are common. CNS effects like ataxia, disorientation, seizures, encephalopathy and psychotic manifestations are rare and reversible.

Uses

Mefloquine is indicated only in MDR strains of *falciparum* malaria - 20 mg/ kg, single dose or in two divided doses. Mefloquine can also be used in the prophylaxis of multidrug resistant malaria in travellers (250 mg/week).

Halofantrine

Halofantrine is schizonticidal against erythrocytic forms of all *Plasmodium* species

Table 44.1: Preferred antimalarials in the treatment and prophylaxis of malaria

Malaria	Drug therapy
Chloroquine sensitive strains	
<i>Treatment</i>	Chloroquine Oral - 600 mg base stat, 300 mg after 6 hr, 300 mg/ day for next 2 days or 600 mg (4 tabs) <i>stat</i> . 600 mg (4 tabs) after 24 hr, 300 mg (2 tabs) after 48 hr.
<i>Prophylaxis</i>	Chloroquine 2 tabs/week; start 1 week before and continue for 4 weeks after leaving the endemic area
Chloroquine resistant and MDR strains	
<i>Treatment</i>	Choices are: - Quinine Oral - 600 mg TDS for 3 days Severe cases IV 10 mg/kg 8 hourly followed by one of the following - Doxycycline 100 mg BD for 7 days - or - Pyrimethamine + sulfadoxine 3 tabs as a single dose on the last day of quinine therapy. - Mefloquine 15 mg/kg single dose (Max 1000 mg) - Artemisinin 100 mg BD on first day, 50 mg BD for next 5 days - Atovaquone + proguanil 250 mg daily for 3 days 100 mg daily for 3 days
<i>Prophylaxis</i>	- Mefloquine 250 mg weekly; start 1 week before and continue for 4 weeks after leaving the area - Doxycycline 100 mg daily; start 2 days before and continue for 4 weeks after leaving the area

including MDR strains of *P. falciparum*. Actions are similar to mefloquine but the disadvantages are that

- The response to oral dosage is unpredictable due to variable absorption toxicity due to good absorption or therapeutic failure due to poor absorption may result.
- It is used as an alternative in MDR strains of falciparum malaria.
- Cannot be given parenterally.
- It can cause cardiotoxicity apart from GI disturbances.

Primaquine

Primaquine is effective against all forms of the malarial parasite except erythrocytic forms.

- It destroys the parasite in the liver cells and prevents the invasion of erythrocytes – causal prophylactic. But it is generally not used for this purpose.
- Primaquine destroys the hypnozoites (exoerythrocytic form) in the liver and thereby prevents relapse of *P. vivax* and *P. ovale* malaria.
- It is also effective against the gametocytes of all four species of the malarial parasite.
- It has weak and insignificant activity against the erythrocytic forms.

Its mechanism of action is not known. Primaquine is completely absorbed orally. It is well tolerated in therapeutic doses. Epigastric distress can occur. It may cause haemolysis in patients with G₆PD deficiency.

Primaquine is used for *radical cure* along with a blood schizontocide in *P. vivax* and *ovale* 15 mg /day for 14 days and as a gametocidal agent in *P. falciparum* malaria - 45 mg single dose.

Bulaquine is an analog of primaquine developed in India (CDRI, Lucknow). It is claimed that patients require fewer days (5 days) of antirelapse therapy when compared to primaquine. But further

extensive clinical trials are required to prove its clinical benefits.

Etaquine and *tafenoquine* are other longer acting analogs of primaquine under trial.

FOLATE ANTAGONISTS

Pyrimethamine is effective against the erythrocytic forms of all 4 species of plasmodia but it is slow acting.

Mechanism of Action Pyrimethamine is a dihydrofolate reductase inhibitor (Fig 44.2). When given with sulfadoxine (a sulfonamide), the combination is synergistic and the development of resistance is slower. Pyrimethamine can also be combined with dapsone.

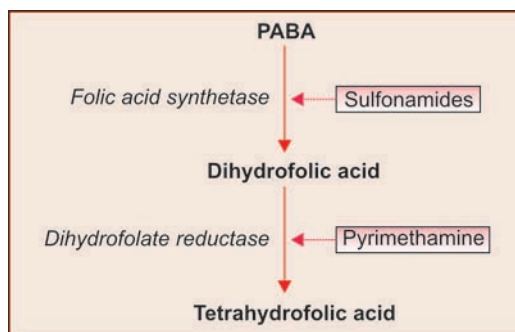


Fig. 44.2: Sequential blockade in folic acid synthesis

Pyrimethamine is quite safe, the combination may cause nausea, rashes and in high doses megaloblastic anaemia. Sulfadoxine may cause serious allergic reactions including Stevens Johnson syndrome.

Uses

1. Malaria

- *Acute attacks* – Pyrimethamine + sulfadoxine combination is used as an alternative in uncomplicated, chloroquine resistant falciparum malaria. It is also used as an adjunct to quinine in acute attacks of malaria.
- *Prophylaxis*–1-2 tablets once weekly for prophylaxis against MDR falciparum

malaria—when a person is visiting an endemic area.

2. *Toxoplasmosis*—Pyrimethamine + sulfadoxine combination is the treatment of choice for *Toxoplasma gondi* infection. Pyrimethamine is given as 200 mg bolus dose followed by 50 mg daily for 4 to 6 weeks along with sulfadoxine 4 g/day. Leucovorin (folinic acid) should be given 10 mg daily to prevent severe folate deficiency.

Chloroguanide (Proguanil) is a schizontocide with causal prophylactic activity against the pre-erythrocytic forms of the malaria parasite. It is used -

- with atovaquone in the treatment of MDR falciparum malaria.
- for causal prophylaxis of falciparum malaria
- as an alternative to pyrimethamine-sulfadoxine for prophylaxis of MDR falciparum malaria.

Atovaquone – is a naphthaquinone, effective against the erythrocytic forms of plasmodia. When combined with proguanil, the activity is synergistic and development of resistance is less common.

Mechanism of action– Atovaquone inhibits the mitochondrial electron transport and collapses the mitochondrial membrane in the malarial parasite. Proguanil potentiates this action.

Atovaquone is also effective against *T. gondii* and *P. carinii* (*P. jiroveci*) infections.

Adverse effects include vomiting, headache and abdominal pain. It is contraindicated in pregnancy.

Uses Atovaquone + Proguanil can be used in the treatment of chloroquine resistant and multi drug-resistant falciparum malaria. Atovaquone 250 mg + proguanil 100 mg daily for three days. Atovaquone may also be used in *P. carinii* infection as an alternative to cotrimoxazole.

Artemisinin and Derivatives

Artemisinin is a sesquiterpine lactone obtained from the plant *Artemisia annua* which has been used in chinese traditional medicine 'Quinghaosu' for almost 2000 years.

Mechanism of action–Artemisinin interacts with heme resulting in the generation of free radicals that bind to the membrane protein and damages the parasite membrane.

Artemisinin is a potent, rapidly acting, blood schizontocide effective against all the 4 plasmodial species, including MDR *P. falciparum*. It is also effective against gametocytes. It is useful in cerebral malaria. No resistant strains are known so far. Recrudescence (the disease becomes active again after a period of remission) is common due to its short $t_{1/2}$. Combining with mefloquine avoids this. It has been shown that it can be safely used in pregnancy.

Artesunate (oral, IM, IV, rectal) and artemether (IM, oral) artemisinin(oral) and arteether (IM) are the compounds used . Arteether is longer acting - given 150 mg (IM) for 3 days.

Artemisinin and derivatives are the best tolerated antimalarials—mild GI symptoms, fever, itching and bradycardia are reported. **Uses** Acute attacks of MDR falciparum malaria and cerebral malaria. Artemisinin can be used even in pregnancy.

Dose Artemisinin - Orally 100 mg BD on first day, 50 mg BD for the next 4 days and in more severe cases, artesunate IV 120 mg on the first day, 60 mg daily for the next 4 days; mefloquine (25 mg/kg) is given on the second day.

Newer Antimalarials Lumefantrine and pyronaridine were synthesized in China. Both are effective against erythrocytic forms of the malaria parasite. Both have poor oral bioavailability. Lumefantrine is combined with artemisinin/mefloquine in the treatment of MDR falciparum malaria.

Drugs Used in Amoebiasis, Leishmaniasis and Trypanosomiasis

ANTIAMOEBIIC DRUGS

Amoebiasis caused by the protozoan *Entamoeba histolytica* is a tropical disease common in developing countries. It spreads by faecal contamination of food and water. Though it primarily affects colon, other organs like liver, lungs and brain are the secondary sites. Acute amoebiasis is characterised by bloody mucoid stools and abdominal pain. Chronic amoebiasis manifests as anorexia, abdominal pain, intermittent diarrhoea and constipation. Cyst passers or carriers are symptom free.

Classification

1. *Drugs effective in both intestinal and extraintestinal amoebiasis*
Metronidazole, Tinidazole, Secnidazole, Ornidazole, Satranidazole, Emetine, Dehydroemetine.
2. *Drugs effective only in intestinal amoebiasis (Luminal amoebicides)*
Diloxanide furoate, Quiniodochlor, Iodoquinol, Tetracylines.
3. *Drugs effective only in extraintestinal amoebiasis*
Chloroquine

Metronidazole

Metronidazole a nitroimidazole, is a powerful amoebicide. Apart from this it also inhibits *Trichomonas vaginalis*, *Giardia lamblia* and *Balantidium coli*. Anaerobic bacteria are also sensitive.

Mechanism of action Metronidazole is a prodrug. Susceptible microorganisms reduce the nitro group of metronidazole by a nitroreductase and convert it to a cytotoxic derivative which binds to DNA and inhibits protein synthesis. Aerobic bacteria lack this nitroreductase and are therefore not susceptible to metronidazole.

Pharmacokinetics Metronidazole is well-absorbed and reaches adequate concentrations in the CSF; has a plasma $t_{1/2}$ - 8 hr. It is metabolised in the liver by oxidation and glucuronide conjugation.

Adverse effects Gastrointestinal effects like nausea, anorexia, abdominal pain and metallic taste in the mouth are the most frequent. Headache, stomatitis, glossitis, furry tongue; dizziness, insomnia, ataxia, vertigo and rarely peripheral neuropathy can occur. Pruritus, urticaria and skin rashes can also occur. High doses can cause convulsions.

Hence metronidazole should be cautiously used in patients with neurological diseases and severe hepatic dysfunction. It is contraindicated in pregnancy. Intravenous injection can cause thrombophlebitis. This can be avoided by adequate dilution of the drug solution.

Drug Interactions

- Metronidazole can produce a disulfiram-like reaction in patients taking alcohol. Hence patients should be advised to avoid alcohol while on metronidazole.
- Drugs like cimetidine which are microsomal enzyme inhibitors, enhance plasma levels of metronidazole resulting in toxicity.

Preparations

Metronidazole is available as 200, 400 mg tablets; 200 mg /5 ml suspension; 500 mg / 100 ml inj and 1% gel and ointment.

Uses

1. Anaerobic infections
 - (a) *Oral infections*—Metronidazole and its congeners are one of the most commonly used antimicrobial agents in dentistry because anaerobes are an important component of the oral flora. Hence most acute odontogenic infections are caused by a combination of aerobic and anaerobic bacteria. Metronidazole is the drug of choice for most odontogenic infections especially those not controlled by penicillins. Odontogenic infections like acute periapical abscess, periodontitis, acute ulcerative gingivitis, pericoronitis and other oral infections and salivary gland infections are treated with metronidazole (200-400 mg TDS) in combination with an antibiotic effective against aerobes like a penicillin or a macrolide. Clindamycin

being effective against gram-positive and anaerobic bacteria is an alternative.

- (b) *Anaerobic infections at other sites*—Intra-abdominal infections, brain abscesses, genitourinary infections are often mixed infections with aerobes and anaerobes. Metronidazole is used in combination with other antimicrobials. Metronidazole is given intravenously for serious anaerobic infections. It is also useful for surgical prophylaxis of abdominal and pelvic infections.
2. *Amoebiasis*—Metronidazole is the drug of choice in all forms of amoebiasis in the dose of 400-800 mg TDS for 7-10 days. But it does not eradicate the cysts.
 3. *Trichomonas vaginitis*—Metronidazole 200 mg TDS for 7 days is the drug of choice.
 4. *Giardiasis*—Metronidazole given 200 mg TDS for 7 days is the treatment of choice.
 5. *H. pylori infections* in peptic ulcer patients can be treated with a combination of metronidazole, clarithromycin and omeprazole/ranitidine.
 6. *Pseudomembranous colitis* due to *Clostridium difficile*—responds to metronidazole.
 7. *Dracunculosis* Metronidazole facilitates extraction of the guinea worm.
 8. *Topical preparations* - like gel and ointment are used in skin infections and acne.
- Tinidazole* is longer-acting and is better tolerated than metronidazole due to fewer side effects. It can be given 2 g once daily for 3 days in amoebiasis and as a single dose for most other indications of metronidazole. *Secnidazole* is longer-acting ($t_{1/2}$ 18-30 hrs) and can be given as a single 2 g dose for most indications of metronidazole. *Ornidazole*—is similar to tinidazole and is longer acting. *Satranidazole* – More potent and longer acting than metronidazole. It is claimed to be better tolerated particularly because it does not cause nausea or metallic taste.

Emetine and Dehydroemetine

Emetine and dehydroemetine derived from Ipecac (Brazil root) directly affect the trophozoites but not the cysts. As oral absorption is improper, they are given parenterally. They can be used only in severe amoebiasis but are not preferred due to toxicity. Adverse effects include pain at the injection site, thrombophlebitis, nausea, vomiting, diarrhoea and cardiotoxicity.

Diloxanide Furoate

Diloxanide furoate is directly amoebicidal. Flatulence, nausea and occasionally abdominal cramps and rashes can occur. It is used alone in asymptomatic cyst passers, mild intestinal amoebiasis and along with a nitroimidazole—for the cure of amoebiasis, because diloxanide eradicates cysts. It is given orally—500 mg TDS for 10 days. It is also available in combination with metronidazole (DYRADE-M).

Chloroquine

Chloroquine attains high concentration in the liver, is directly toxic against trophozoites and is therefore useful in hepatic amoebiasis. As chloroquine is completely absorbed from the small intestines, it is not effective against amoebae in the colon. It is used (300 mg/day for 2-3 weeks) as an alternative to metronidazole in hepatic amoebiasis. A luminal amoebicide should also be given.

Iodoquinol and Quiniodochlor

Iodoquinol and quiniodochlor (8-hydroxyquinolines) are directly acting luminal amoebicides. They were used for eradication of cysts but are not preferred now due to their toxicity like subacute myelo-optic neuropathy.

Tetracyclines The older tetracyclines are not well-absorbed and large amounts reach the colon—hence these are useful in intestinal amoebiasis. They inhibit the intestinal flora and break the symbiosis between them and the amoebae. Tetracyclines are used as adjuvants in chronic cases.

Treatment of Different Forms of Amoebiasis

1. *Acute intestinal amoebiasis*—one of the following can be given.
 - Metronidazole 400-800 mg TDS for 5-7 days (METROGYL, FLAGYL)
 - or
 - Metronidazole 2.4 g OD for 3 days
 - or
 - Tinidazole 2 g OD for 3 days (TINIBA)
 - or
 - Secnidazole 2 g single dose (SECZOL, SECNIL)

This should be followed by diloxanide furoate 500 mg TDS for 10 days to eradicate the cysts.

2. *Chronic amoebiasis* Diloxanide furoate 500 mg TDS for 10 days or tetracycline 250 mg qid for 10 days.
3. *Hepatic amoebiasis* requires intensive treatment for the complete eradication of the parasite from the liver in order to avoid relapses. A course of metronidazole or tinidazole are the first line drugs. In addition chloroquine may be given to ensure complete destruction of the liver forms. A course of diloxanide furoate should follow in order to eradicate the cysts.

TREATMENT OF PNEUMOCYSTOSIS

Pneumocystis carinii is a micro-organism having features of both protozoa and fungi though now considered by most to be a fungus. Recent studies have shown that pneumocystosis in human beings is caused by *Pneumocystis jiroveci* while *P. carinii* causes pneumocystosis in animals.

It is now known to cause opportunistic infections particularly pneumonia in patients with AIDS which can often be fatal.

Drugs used in the treatment of pneumocystosis include

- Cotrimoxazole - high oral dose of Trimethoprim 20 mg/kg + sulphamethoxazole 100 mg/kg daily.
- Pentamidine - 4 mg/kg daily for 14 days parenterally.
- Atovaquone - as an alternative to cotrimoxazole.

LEISHMANIASIS

Leishmaniasis is caused by protozoa of the genus *Leishmania*. Kala-azar or visceral leishmaniasis is caused by *Leishmania donovani*; oriental sore by *L. tropica* and mucocutaneous leishmaniasis by *L. braziliensis*. The infection is transmitted by the bite of the female sandfly phlebotomus. It is endemic in Bihar. Drugs used in leishmaniasis include:

Antimony compounds Sodium stibogluconate

Meglumine antimonate

Diamidines Pentamidine

Other drugs Amphotericin B, Ketoconazole,

Allopurinol, Paramomycin

Antimony Compounds

Sodium stibogluconate, a pentavalent antimonial is the most effective drug in kala-azar. It is also effective in mucocutaneous and cutaneous leishmaniasis. It is given as a 4% solution in the dose of 10-20 mg/kg IM (gluteal region) or IV for 20 days. Mechanism of action is unknown.

Adverse effects include a metallic taste in the mouth, nausea, vomiting, diarrhoea, headache, myalgia, arthralgia, pain at the injection site, bradycardia, skin rashes, haematuria and jaundice. Some cases of sudden death due to shock have occurred. ECG should be monitored as arrhythmias can occur during the later days of therapy.

Though sodium stibogluconate is quite effective, resistance has been encountered in endemic areas like Bihar.

Meglumine antimonate and *ethyl stibamine* can also be used in all forms of leishmaniasis.

Pentamidine is an aromatic diamidine effective against *Leishmania donovani*, trypanosomes, *Pneumocystis carinii* and some fungi. Given intramuscularly the drug is rapidly absorbed but very little reaches the CNS. Dose 4 mg/kg deep IM/slow IV on alternate days for 5-25 weeks.

Adverse effects Pentamidine liberates histamine which is responsible for vomiting, diarrhoea, flushing, pruritis, rashes, tachycardia and hypotension apart from pain at the injection site. Other effects include hepatotoxicity, renal impairment, ECG changes and in some patients diabetes mellitus may be precipitated.

Uses

1. *Leishmaniasis* Pentamidine can be used in visceral leishmaniasis as an alternative to sodium stibogluconate.
2. *Trypanosomiasis* Pentamidine can be used as an alternative to suramin or along with suramin in trypanosomiasis. It can also be used for chemoprophylaxis against African trypanosomiasis.
3. *Pneumocystosis* Pentamidine is an alternative in *Pneumocystis jiroveci* infections in patients unable to tolerate cotrimoxazole.

Other Drugs

Amphotericin B (page 300) has been tried in leishmaniasis in the endemic areas where antimonials may be ineffective.

Ketoconazole inhibits ergosterol synthesis in the leishmania and is effective in cutaneous leishmaniasis.

Allopurinol (page 188) In leishmania, allopurinol is converted to a metabolite which inhibits protein synthesis. It may be used along with antimonials.

Dose: 300 mg 3-4 times a day for 2-4 weeks.

Paramomycin (aminosidine) is an amoebicidal drug which is also found to be effective in leishmaniasis. It is useful in all forms of leishmaniasis. It can be used alone or in combination with antimonials.

TRYPANOSOMIASIS

Trypanosomiasis is caused by protozoa of the genus *Trypanosoma*. African trypanosomiasis or sleeping sickness is caused by *T. gambiense* and *T. rhodesiense* while South American trypanosomiasis is caused by *T. Cruzi*. Drugs used in trypanosomiasis are suramin, pentamidine, melarsoprol, eflornithine, nifurtimox and benznidazole. *Suramin sodium*

is the drug of choice for early stage of trypanosomiasis but it does not cross the BBB and therefore cannot be used in later stages of the disease. It is also useful for the prophylaxis but pentamidine is preferable. Suramin is given IV; it is extensively bound to plasma proteins and may be traced for nearly 3 months in the plasma. Suramin is also effective in eradicating adult forms of *Onchocerca volvulus*.

Toxicity is high; vomiting, shock and loss of consciousness may follow IV injections. Rash, neuropathies, haemolytic anaemia and agranulocytosis may also occur.

Melarsoprol is the preferred drug in later stages of trypanosomiasis which is associated with encephalitis and meningitis.

Eflornithine is used as an alternative in CNS trypanosomiasis. *Nifurtimox* and benznidazole are useful in Chaga's disease (American trypanosomiasis).

Anthelmintics

Worm infestations are more common in the developing countries. It is seen in people with poor hygiene. Anthelmintics are deworming agents. A *vermicidal* kills while a *vermifuge* promotes expulsion of worms.

Benzimidazoles

Benzimidazoles include thiabendazole, mebendazole and albendazole. Thiabendazole the first agent of this group was discovered in 1961 but now the newer ones, mebendazole and albendazole are more commonly used due to lesser toxicity.

Mebendazole

Mebendazole a broad spectrum anthelmintic cures roundworm, hookworm, pinworm and strongyloides infestations. The eggs and larvae are also destroyed. The dead parasites are slowly expelled from the gut over several days.

Mechanism of action Benzimidazoles bind to β -tubulin with high affinity and inhibit glucose uptake in the parasite.

Pharmacokinetics Mebendazole is poorly absorbed from the gut and also undergoes first pass metabolism - bioavailability around 20%. Fatty food enhances absorption. Mebendazole is extensively bound to plasma proteins and is metabolised by the liver.

Mebendazole is given orally 100 mg twice a day for 3 days.

Adverse effects Mebendazole is well-tolerated; nausea, abdominal pain and diarrhoea are seen in heavy infestations. Large doses may rarely cause headache, dizziness, loss of hair and granulocytopenia. It may rarely provoke abnormal migration of the roundworms which may come out through the mouth or nose.

Uses Mebendazole is used in the treatment of roundworm, hookworm, pinworm, tapeworm, trichuriasis and hydatid disease. It is of special value in multiple worm infestations. (Table 46.1)

Albendazole

Albendazole is a congener of mebendazole with actions and mechanism of action similar to mebendazole but it has several advantages over it.

Advantages over Mebendazole

- Albendazole is better tolerated
- Effective in single dose
- Superior to mebendazole in hook worm and thread worm infections, hydatid disease and neurocysticercosis
- Albendazole also has some activity against *Trichomonas vaginalis*, *Giardia lamblia* and *Wuchereria bancrofti*.
- The active metabolite of albendazole achieves a higher concentration (100 times more) than mebendazole.

Table 46.1: Preferred drugs for helminthiasis

Worms	Drugs of choice	Alternative drugs
1. Roundworm (<i>Ascaris lumbricoides</i>)	Mebendazole / albendazole / pyrantel	Piperazine
2. Hookworms (<i>Ancylostoma duodenale</i> , <i>Necator americanus</i>)	Mebendazole / albendazole	Pyrantel
3. Pinworm (<i>Enterobius vermicularis</i>)	Mebendazole / albendazole / pyrantel	Piperazine
4. Whipworm (<i>Trichuris trichura</i>)	Mebendazole	Albendazole
5. Strongyloides stercoralis	Albendazole	Thiabendazole
6. Guinea worm (<i>Dracunculus medinensis</i>)	Metronidazole	Mebendazole
7. Tapeworms (<i>Taenia saginata</i> , <i>Taenia solium</i> , <i>H. nana</i> , <i>D. latum</i>)	Niclosamide / praziquantel	Albendazole
Neurocysticercosis	Albendazole	Praziquantel
8. Hydatid disease (<i>E. granulosus</i> , <i>E. multilocularis</i>)	Albendazole	Mebendazole
9. Filariasis (<i>Wuchereria bancrofti</i> , <i>Brugia malayi</i>)	Diethylcarbamazine + albendazole	Ivermectin albendazole
10. Schistosomes	Praziquantel	—
11. Onchocerca volvulus	Ivermectin	—
12. Fasciola hepatica (Sheep liver fluke)	Bithionol	—

Pharmacokinetics—Albendazole is rapidly absorbed from the gut and fatty food enhances its absorption. It penetrates well into tissues including hydatid cyst. It is rapidly metabolised in the liver and excreted in urine.

Adverse effects - are minor similar to mebendazole. Nausea, diarrhoea, abdominal pain, headache and dizziness can occur. High doses used over a long time can cause jaundice, fever, weakness, alopecia and granulocytopenia. Albendazole is teratogenic in animals and therefore should not be given in pregnancy.

Uses

1. Albendazole is the drug of choice in roundworm, hookworm, pinworm, trichuriasis infestations in a single 400 mg dose. Dose should be repeated after 2 weeks in pinworm infestation to prevent

reinfection from ova that have matured later.

2. Trichinosis, tapeworms and strongyloidosis require 400 mg daily for 3 days.
3. Neurocysticercosis—Albendazole is the drug of choice in a dose of 400 mg twice daily but the duration depends on the number of cysts and may vary from 3 to 28 days. Glucocorticoids should be given before starting albendazole to prevent immunological reactions to the dead parasite.
4. Hydatid disease—Albendazole is the drug of choice; 400 mg twice daily is given for 4 weeks. If needed, the course may be repeated after 2 weeks. When the cysts are removed by surgery, albendazole is more effective in providing cure.
5. Filariasis—Combination of albendazole (400 mg) with diethylcarbamazine (6 mg/kg) or ivermectin (0.3 mg/kg) given as a

single dose is found to be effective in *W. bancrofti* in suppressing microfilariae for one year. This also prevents the spread of filariasis and may be continued once a year for 5-6 years.

Thiabendazole

Thiabendazole a benzimidazole, acts like mebendazole. But due to frequent side effects, it is not preferred. Dizziness, anorexia, vomiting, diarrhoea, drowsiness, paraesthesia, bradycardia, hypotension, convulsions and liver damage can occur. It is used as an alternative to albendazole in strongyloidosis and cutaneous larva migrans.

Pyrantel Pamoate

Pyrantel pamoate is effective against roundworm, hookworm and pinworms. It stimulates the nicotinic cholinergic receptor in the worm leading to persistent depolarisation and spastic paralysis (depolarising neuromuscular blocker). The paralysed worms are expelled.

It is well-tolerated; occasional abdominal pain, headache, rashes, weakness and dizziness may occur. Dose: 10-15 mg/kg single dose.

Uses Pyrantel pamoate is used in the treatment of roundworm, hookworm and pinworm infestations.

Oxantel pamoate an analog of pyrantel pamoate is effective in the treatment of trichuriasis infection.

Piperazine Citrate

Piperazine citrate is effective in roundworm and pinworm infestations. It competitively blocks the actions of acetylcholine and thereby contractions in the worms. Flaccid paralysis results and the worms are expelled.

Adverse effects are mild—gastrointestinal symptoms, headache and dizziness are seen occasionally. Piperazine citrate is indicated for roundworm and pinworm infestations. It is also safe in pregnancy.

Levamisole

Levamisole is effective against roundworms and hookworms and can be used as an alternative drug in these infestations. It is well-tolerated and is effective in a single dose. It is also an immunomodulator.

Niclosamide

Niclosamide is effective against most tapeworms. The segments of the dead tapeworms are partly digested and in case of *T. solium*, the ova released from these segments may develop into larvae and reach various organs resulting in visceral cysticercosis. Purge may be given 2 hours after niclosamide to wash off the worms and avoid cysticercosis. The scolex detected in the stool ensures eradication.

Niclosamide is well-tolerated. Abdominal discomfort and rarely pruritus and rashes may occur.

Uses Niclosamide is the drug of choice in infestations by tapeworms like *T. solium*, *T. saginata*, *H. nana* and *D. latum*. It is also an alternative drug in intestinal fluke infestation.

Praziquantel

Praziquantel is effective against schistosomes of all species, most other trematodes and cestodes including cysticercosis. It is effective as a single oral dose in most infestations. It increases cell membrane permeability to calcium resulting in contraction followed by paralysis and the worms are expelled.

Adverse effects are mild and include GI disturbances, headache, dizziness, drowsiness, rashes and myalgia.

Uses

1. *Schistosomiasis* Praziquantel is the drug of choice in all forms of schistosomiasis.
2. *Tapeworms* Single dose (10 mg/kg) of praziquantel is effective in all tapeworm infestations. In *T. solium* it has the

advantage that it kills the larvae and therefore visceral cysticercosis is avoided.

3. *Neurocysticercosis* Praziquantel is an alternative to albendazole.

Diethylcarbamazine

Diethylcarbamazine (DEC) is the drug of choice in filariasis. It immobilizes the microfilariae resulting in their displacement in the tissues and also alters their surface structure making them more susceptible to the host defense mechanisms. Microfilariae rapidly disappear from the blood except those present in hydrocele and nodules.

Adverse effects are mild; anorexia, nausea, vomiting, dizziness and headache; allergic reactions with itching, rashes and fever due to release of antigens from the dying worms may occur. Antihistamines are given with DEC to minimize these reactions. DEC can be given during pregnancy.

Uses

- *Filariasis* DEC is the drug of choice (2 mg/kg TDS for 21 days). In 7 days patients are rendered non-infective to mosquitoes as microfilariae rapidly disappear. But adult worms may need repeated courses.
- *Tropical eosinophilia* (2 mg/kg TDS for 7 days). Symptoms rapidly disappear.

Ivermectin

Ivermectin is a semisynthetic analog of avermectin B obtained from *streptomyces avermitilis*. Ivermectin is effective against many nematodes, arthropods and filariae that infect animals and human beings. Ivermectin is very effective against the microfilaria of *Onchocerca volvulus*. It is microfilaricidal and also blocks the release of microfilariae from the uterus of adult worms. There is a rapid decrease in the microfilarial count in the skin and eyes.

Ivermectin is believed to act by paralysing the worms by binding to GABA-gated chloride channels and enhancing GABA activity.

Ivermectin is as effective as DEC against *W. bancrofti* and *B. malayi*. It is also effective against *Strongyloidis stercoralis*, *Ascaris lumbricoides*, and *cutaneous larva migrans*.

Adverse effects—Ivermectin is well tolerated. Apart from nausea and vomiting, allergic reactions can result due to hypersensitivity to the dying microfilarial proteins (mazotti reaction).

Ivermectin should not be used with other drugs that influence GABA activity (e.g. benzodiazepines, valproic acid) in patients with meningitis and sleeping sickness as these conditions impair the blood brain barrier.

Uses

1. Ivermectin is the preferred drug in the treatment of onchocerciasis.
2. Ivermectin is also useful in the treatment of lymphatic filariasis.
3. A single dose of 400 mg/kg ivermectin with 400 mg albendazole is given once a year for mass chemotherapy of lymphatic filariasis.
4. Strongyloidiasis – A single dose of 200 mg/kg is curative in strongyloidiasis. However the dose is to be repeated on the second day.
5. Ivermectin is also useful in cutaneous larva migrans, ascariasis and in scabies.

Metrifonate is a prodrug that is converted to dichloroovas—an organophosphorus insecticide. Metrifonate is used as an alternative to praziquantel in the treatment of *Schistosoma haematobium* infections.

Oxamniquine is effective against *S. mansoni* and is used as an alternative to praziquantel in the treatment of *S. mansoni* infections.

Bithionol is the drug of choice in the treatment of *Fasciola hepatica* infections.

Cancer Chemotherapy

Cancer is one of the major causes of death. The treatment of cancers is still unsatisfactory due to certain characteristics of the cancer cells—like capacity for uncontrolled proliferation, invasiveness and metastasis. Moreover the cancer cells are our own cells unlike microbes, which means that, drugs which destroy these cells also can affect normal cells. The host defence mechanisms which help us in infections is not doing so in cancers as these cancer cells are also host cells. Moreover, the cancer cells can be in a resting phase during which they are not sensitive to anticancer drugs but can start multiplying later—resulting in recurrence. These features have made cancer chemotherapy more difficult.

Phases of cell cycle—Four phases of cell cycle are G_1 , S, G_2 , and M (Fig 49.1). G_1 is the presynthetic phase and the duration is variable. During the S phase the synthesis of DNA occurs and hence the activity of replicating enzymes like DNA and RNA polymerases, topoisomerases, thymidine kinases and dihydrofolate reductases are maximum at this phase of 12 to 18 hours duration. G_2 is the postsynthetic phase (1 to 8 hrs) and in the M phase (1 to 2 hrs) the mitosis takes place. The daughter cells may start dividing or may enter into a dormant phase called G_0 . The knowledge of cell cycle may be used for staging and scheduling treatment

because different drugs act at different stages of the cell cycle. However, some drugs are cell cycle non-specific (Table 47.1).

Common Adverse Effects to Anticancer Drugs

Since most anticancer drugs act on the rapidly multiplying cells, they are also toxic to the normal rapidly multiplying cells in the bone marrow, epithelial cells of the skin and mucous membranes, lymphoid organs and gonads. Thus the common adverse effects are:

1. *Bone marrow depression* resulting in leukopenia, anaemia, thrombocytopenia and in higher doses—aplastic anaemia. In such patients, infections and bleeding are common.

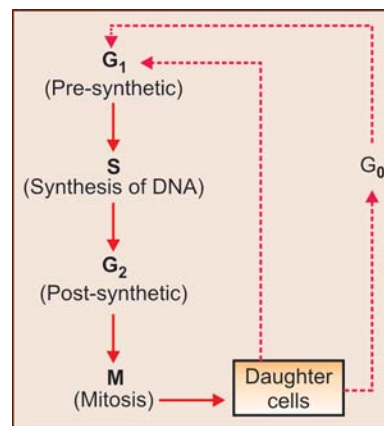


Fig 47.1: Phases of cell cycle

Drugs used in cancers may be classified as follows:

CLASSIFICATION

1. <i>Alkylating agents</i>	
<i>Nitrogen mustards</i>	Mechlorethamine, cyclophosphamide, ifosfamide, chlorambucil, melphalan
<i>Ethylenimines</i>	Thio-TEPA
<i>Alkyl sulfonate</i>	Busulfan
<i>Nitrosoureas</i>	Carmustine, streptazocin
<i>Triazine</i>	Dacarbazine
2. <i>Antimetabolites</i>	
<i>Folate antagonist</i>	Methotrexate
<i>Purine antagonist</i>	6-Mercaptopurine thioguanine, azathioprine pentostatin, fludarabin, cladribin.
<i>Pyrimidine antagonist</i>	5-Fluorouracil, floxuridine, cytarabine (cytosine arabinoside) gemcitabine
3. <i>Antibiotics</i>	Actinomycin-D (Dactinomycin), daunorubicin, doxorubicin, bleomycin, mitomycin-C, mithramycin
4. <i>Epipodophyllotoxins</i>	Etoposide, teniposide
5. <i>Camptothecins</i>	Topotecan, irinotecan
6. <i>Taxanes</i>	Paclitaxel, docetaxel
7. <i>Vinca alkaloids</i>	Vincristine, vinblastine, vinorelbine
8. <i>Miscellaneous</i>	Procarbazine, mitotane, l-asparaginase, cisplatin, interferon alpha, imatinib
9. <i>Hormones and their antagonists</i>	Glucocorticoids, androgens, antiandrogens, estrogens, antiestrogens, progestins, aromatase inhibitors

2. Other proliferating cells

- Oral lesions including stomatitis and glossitis can be painful and bleeding from oral lesions are common following the use of anticancer drugs. Since they also depress the bone marrow, even minor dental procedures can cause severe bleeding because platelet count gets reduced. Good oral hygiene should be maintained. Antiseptic mouth washes may be given till the bone marrow recovers.
- GIT-esophagitis and proctitis can be painful. Diarrhoea and ulcers throughout the gut are common following the use of anticancer drugs.
- Alopecia (loss of hair) - partial to total alopecia is seen following treatment with most anticancer drugs but it is reversible and the hair grows after the chemotherapy is completed.
- Reduced spermatogenesis in men and amenorrhoea in women (due to damage to the germinal epithelium) can occur.

3. *Immediate adverse effects* Nausea and vomiting are very common with most cytotoxic drugs. They result from the stimulation of the vomiting centre and CTZ and starts about 4 to 6 hours after treatment and may continue for 1 to 2 days. Prior treatment with powerful antiemetics is required.
4. *Teratogenicity* All cytotoxic drugs are teratogenic and are therefore contraindicated in pregnancy.
5. *Carcinogenicity* Cytotoxic drugs themselves may cause secondary cancers, e.g. leukaemias are common after treatment of Hodgkin's lymphoma.

Apart from the above, the adverse effects unique to some drugs are discussed under individual drugs listed in Table 47.2.

ALKYLATING AGENTS

Actions Alkylating agents exert cytotoxic, immunosuppressant and radiomimetic effects (similar to radiotherapy).

Mechanism of action These drugs form highly reactive derivatives which transfer alkyl groups to various cellular constituents and bind them with covalent bonds. Thus such constituents are not available for normal metabolic reactions. Moreover, alkylation of DNA results in breakage of the DNA strand.

Table 47.1: Cell cycle specific and non-specific drugs

Cell cycle specific drugs	Cell cycle non specific drugs
<i>S phase-</i> Antimetabolites, Doxorubicin, Epipodophyllotoxins, Vinca alkaloids.	Alkylating agents Anticancer antibiotics Cisplatin Procarbazine
<i>G₂ and M Phases -</i> Bleomycin	
<i>M phase -</i> Taxanes, Vinca alkaloids.	

Mechlorethamine is given IV as it is a highly irritant compound. It is used in Hodgkin's (MOPP regime) and other lymphomas.

Cyclophosphamide is converted to its active metabolite aldophosphamide in the body. It can be given orally. Cyclophosphamide causes cystitis due to a metabolite acrolein. This can be prevented by giving IV *Mesna*, irrigating the bladder with acetylcysteine, and by taking in large amounts of fluids. *Mesna* (sodium-2 mercaptoethane sulphonate) and acetylcysteine contain SH groups which bind the toxic metabolites and inactivate them.

Cyclophosphamide is used in Hodgkin's lymphoma, leukaemias in children and as an immunosuppressive agent.

Ifosfamide has actions and toxicities similar to cyclophosphamide except that it is longer acting.

Chlorambucil (LEUKERAN) is very effective against lymphoid series. It is the drug of choice in chronic lymphocytic leukaemia.

Melphalan is given orally in multiple myeloma. Its actions and toxicities are similar to other nitrogen mustards.

Busulfan (MYLERAN) has selective activity against cells of the myeloid series and is the drug of choice in chronic myeloid leukaemia.

Nitrosoureas Carmustine is effective in meningeal leukaemias and brain tumours because it crosses the blood-brain barrier. It is also used in lymphomas and malignant melanoma. *Streptozocin* is an antibiotic. It is used in pancreatic islet cell tumours.

Dacarbazine is useful in malignant melanoma.

ANTIMETABOLITES

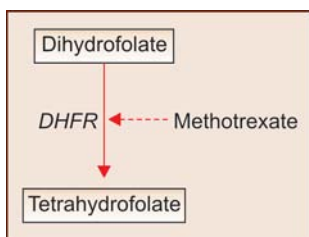
Folate Antagonist

Methotrexate is a folic acid antagonist. It binds to dihydrofolate reductase (DHFR) and prevents the formation of tetrahydrofolate

Table 47.2: Specific adverse effects of some anticancer drugs

<i>Drugs</i>	<i>Specific adverse effects</i>	<i>Other prominent adverse effects</i>
Cyclo-phosphamide	Cystitis, stomatitis	Bone marrow depression, alopecia, vomiting, amenorrhoea, teratogenicity
Busulfan	Pulmonary fibrosis, stomatitis	Bone marrow depression, alopecia, vomiting, amenorrhoea, teratogenicity
Cisplatin	Ototoxicity	Renal dysfunction
Bleomycin	Pulmonary fibrosis, oedema of hands	Stomatitis, alopecia
Daunorubicin	Cardiotoxicity, red coloured urine	Bone marrow depression, alopecia
Doxorubicin	Cardiotoxicity	Bone marrow depression, alopecia
Mithramycin (Plicamycin)	Hepatotoxicity	Thrombocytopenia
Vincristine	Neurotoxicity, Peripheral neuritis, mental depression	Muscle weakness, alopecia
Asparaginase	Pancreatitis, hepatotoxicity,	Allergic reactions
Mitotane	Dermatitis, mental depression	Diarrhoea

(THF). This THF is a coenzyme essential in several reactions in protein synthesis. The deficiency results in inhibition of protein synthesis. Thus rapidly multiplying cells are the most affected.



Actions Cytotoxic actions—methotrexate mainly affects the bone marrow, skin and gastrointestinal mucosa and other rapidly dividing cells.

It also has immunosuppressant and some anti-inflammatory properties.

Methotrexate toxicity can be largely prevented by administering folinic acid. This folinic acid (also called leucovorin or citrovorum factor) gets converted to a form of THF that can be utilised by the cells.

Uses Methotrexate is curative in choriocarcinoma and is useful in acute leukaemias, breast cancer and soft tissue sarcomas. It is also used in rheumatoid arthritis and psoriasis.

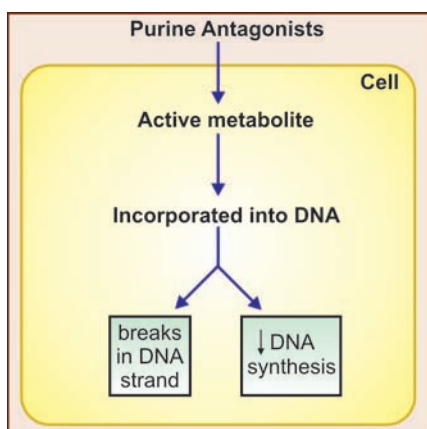
Purine Antagonists

6 Mercaptopurine, thioguanine, azathioprine, fludarabine, pentostatin and cladribine are purine antagonists.

Mechanism of action Purine antagonists enter the cells and get converted to active metabolites (triphosphates in most compounds) which are incorporated into DNA. They cause breakages in DNA strands and inhibit protein synthesis.

Mercaptopurine (6-MP) undergoes extensive first pass metabolism. It is metabolised by xanthine oxidase. Adverse effects include bone marrow depression, anorexia, nausea, vomiting, stomatitis, jaundice and dermatitis.

Drug interaction 6-Mercaptopurine is metabolised by xanthine oxidase. Allopurinol inhibits xanthine oxidase and thus prolongs the action of 6-MP.



Mechanism of action of purine antagonists

Uses 6-MP is used in acute leukaemias in children, choriocarcinoma and some solid tumours.

Thioguanine is effective orally and is used in acute leukemias particularly acute granulocytic leukaemia.

Fludarabine is converted to an active triphosphate derivative which inhibits DNA synthesis. It is also incorporated into DNA and causes breakage and termination of the DNA chain. Adverse effects include nausea, vomiting, anorexia, bone marrow depression, and neurotoxicity.

Fludarabine is used in the treatment of chronic lymphocytic leukaemia (CLL) and Hodgkin's lymphomas.

Pentostatin obtained from *Streptomyces antibioticus* inhibits the enzyme adenosine deaminase and inhibits DNA synthesis.

Pentostatin can cause nausea, vomiting, diarrhoea, skin rashes and bone marrow suppression.

Pentostatin is used intravenously in the treatment of hairy cell leukaemia and other chronic leukaemias and non-Hodgkin's lymphomas.

Cladribine is the drug of choice in hairy cell leukaemia. It is also useful in CLL, AML and some lymphomas. Cladribine causes mild

bone marrow suppression, nausea, vomiting, weakness and skin rashes.

PYRIMIDINE ANTAGONISTS

Pyrimidine antagonists are converted to active metabolites which resemble natural nucleotides. They compete with natural nucleotides, are incorporated into DNA in place of natural nucleotides and inhibit DNA synthesis.

5-Fluorouracil is a pyrimidine analog. It inhibits the enzyme thymidylate synthetase due to which it inhibits the synthesis of thymine and thereby inhibits DNA synthesis. It is used in carcinoma of the stomach, colon, rectum, breast and ovaries.

Cytosine arabinoside or cytarabine is the most effective agent in acute myelocytic leukaemia. It causes nausea, vomiting and bone marrow depression.

Cytarabine is useful in acute leukaemias particularly myeloid leukaemia and in relapsed cases of acute lymphocytic leukaemia. *Gemcitabine* is a recently developed analog of cytarabine with mechanism of action similar to cytarabine. Adverse effects are

Purine Antagonists

- Purine antagonists get incorporated into DNA and inhibit protein synthesis.
- Mercaptopurine, thioguanine are used in acute leukaemias, fludarabine and pentostatin in CLL and non-Hodgkin's lymphomas; cladribin is the drug of choice in hairy cell leukaemia.
- Purine antagonists share the common adverse effects of anticancer drugs. Fludarabine and pentostatin combination can cause fatal lung toxicity.

milder with flu-like syndrome and mild bone marrow depression. It is used in pancreatic, lung, cervical, ovarian and breast cancers.

ANTIBIOTICS

Actinomycin D (Dactinomycin) acts by inhibiting DNA-dependent RNA synthesis. It is one of the most potent anticancer drugs and is used in Wilms' tumour, rhabdomyosarcoma, choriocarcinoma and some soft tissue sarcomas.

Daunorubicin and *doxorubicin* are anthracyclines. They act by inhibiting DNA synthesis. Cardiotoxicity with hypotension, arrhythmias and CCF, is unique to both these drugs. They also cause vomiting, stomatitis, alopecia and bone marrow depression.

Daunorubicin is used in acute leukaemias while doxorubicin is useful in solid tumours and in acute leukaemias.

Epirubicin and *mitoxantrone* are analogs of doxorubicin which are less cardiotoxic.

Mitomycin C is converted to an alkylating agent in the body. It is used in cancers of the stomach, lungs and cervix.

Bleomycin is obtained from *Streptomyces verticillus*. It binds with iron and forms free radicals and causes breakage in DNA strand. It has the advantage of the unique mechanism of action and is less toxic to the bone marrow—this is advantageous in combination regimens.

Bleomycin is used in solid tumours—testicular tumours, squamous cell carcinoma of the head, neck and oesophagus.

It's most serious toxicity includes pulmonary fibrosis and cutaneous toxicity but does not cause significant bone marrow depression.

Mithramycin (*Plicamycin*) is highly toxic, used in disseminated testicular tumours and in severe hypercalcaemia due to bone cancers. It reduces plasma calcium levels by its action on the osteoclasts.

EPIPODOPHYLLOTOXINS

Etoposide and *teniposide* are plant extracts obtained from the mandrake plant. They bind to topoisomerase II as well as DNA resulting in DNA strand breakages. They are used in testicular and lung cancers.

TAXANES

Paclitaxel was obtained from the bark of the western yew tree. It binds to β -tubulin of microtubules and arrests mitosis. Paclitaxel is given intravenously; it is metabolised by the liver microsomal enzymes. Adverse effects include myelosuppression, myalgia and peripheral neuropathy. *Docetaxel* is more potent and orally effective.

Taxanes are useful in breast cancers and ovarian cancers. They are also found to be effective in the cancers of the head and neck, oesophagus and lungs.

Drugs which cause least/no bone marrow depression	Curable cancers	Tumours resistant to treatment
- Hormones - Vincristine - Bleomycin - L-asparaginase - Cisplatin	- Hodgkin's disease - Choriocarcinoma - Burkitt's lymphoma - Testicular tumours - Wilms' tumour - Acute leukaemias in children - Ewing's sarcoma	- Carcinoma colon - Carcinoma rectum - Melanomas - Pancreatic tumours - Renal cancers - Some lung cancers

CAMPTOTHECINS

Camptothecin the first anticancer agent in this group was found to be too toxic. Its analogs, *topotecan* and *irinotecan* are less toxic and useful. They inhibit topoisomerase I resulting in DNA strand breakages leading to cell death. They act on the S phase of the cell cycle. Both are given intravenously.

Toxicity is milder and includes diarrhoea and reversible bone marrow suppression, nausea, weakness and skin rash. Irinotecan inhibits the enzyme acetylcholinesterase resulting in accumulation of acetylcholine causing excessive salivation, abdominal cramps, miosis, bradycardia and sweating which respond to treatment with atropine.

VINCA ALKALOIDS

Vincristine and vinblastine are obtained from *Vinca rosea*, the periwinkle plant. They bind to microtubules in the mitotic apparatus and arrest cell division in metaphase. They are spindle poisons. The alkaloids differ in toxicity.

Vincristine (*Oncovin*) is neurotoxic while bone marrow depression is less. It is used in leukaemias, Hodgkin's lymphoma, Wilms' tumour and brain tumour.

Vinblastine causes bone marrow depression, alopecia and vomiting. It is used with bleomycin and cisplatin (VBC) in testicular tumours; it is also useful in Hodgkin's lymphoma.

Vinorelbine is a semisynthetic vinca alkaloid used intravenously in lung cancers. It can cause granulocytopenia, nausea, vomiting and paraesthesias.

MISCELLANEOUS

Procarbazine is effective orally in Hodgkin's lymphoma (MOPP regime component). It damages DNA. This may make it carcinogenic.

Cisplatin gets converted to its active form in the cell, inhibits DNA synthesis and causes cytotoxicity. It causes ototoxicity, nephrotoxicity, peripheral neuropathy, nausea, vomiting and anaemia. Anaphylactoid reactions can follow its use. It is relatively less toxic to bone marrow. Cisplatin is used in ovarian and testicular tumours and cancers of the head and neck.

Carboplatin is a less toxic derivative of cisplatin and is better tolerated than cisplatin as adverse effects are milder but it causes myelosuppression.

Oxaliplatin is effective in advanced colorectal cancer and in other cancers like ovarian and cervical cancers.

L-asparaginase The amino acid asparagine is synthesized by normal cells but malignant cells are unable to synthesize asparagine and depend on the host for the supply. Asparaginase is an enzyme that converts asparagine to aspartic acid and deprives the malignant cells of asparagine supplies resulting in inhibition of protein synthesis. It is used in acute leukaemias. It causes nausea, vomiting and CNS depression. Bone marrow suppression is mild.

Imatinib is a recent introduction in cancer chemotherapy. It acts by inhibiting some selective tyrosine kinases which are considered to be involved in the pathogenesis of chronic myeloid leukaemia.

Imatinib is almost completely absorbed when given orally. It can cause skin rashes and elevated serum transaminases. Imatinib is used in chronic myeloid leukaemia.

HORMONES IN CANCER CHEMOTHERAPY

Glucocorticoids Due to their lympholytic action, glucocorticoids are used in acute leukaemias and lymphomas. Rapid clinical improvement is seen but duration can vary

from 2 weeks to 9 months. They are used for initiation of therapy due to their rapid action. Glucocorticoids are also of value in the following:

1. with radiation therapy to reduce radiation oedema
2. in intracranial tumours to reduce cerebral oedema
3. for symptomatic relief in critically ill patients.

Prednisolone or dexamethasone are commonly used.

Oestrogens are useful in (i) prostatic carcinoma as it is an androgen dependent tumour, (ii) breast cancer in males and in postmenopausal women—oestrogens are used in advanced cases where surgery or radiotherapy cannot be employed.

Progestins are useful in the palliative management of endometrial carcinoma.

Androgens are used in the palliative treatment of breast cancer in postmenopausal women along with oophorectomy.

Hormone Antagonists

Aromatase inhibitors The enzyme aromatase catalyzes the conversion of androgens to oestrogens. Inhibitors of aromatase have been found to be effective in breast cancers. Formestane, exemestane, anastrozole, vorozole and letrozole are the aromatase inhibitors used.

Aminoglutethimide and *trilastane* inhibit the conversion of cholesterol to pregnenolone (the first step in corticosteroid synthesis) and thereby inhibit the synthesis of adrenocorticoids. Aminoglutethimide is useful in advanced breast cancers when cancer cells contain oestrogen receptors.

Antioestrogens Tamoxifen is an oestrogen receptor antagonist used in estrogen receptor containing breast cancer (page 356).

GnRH analogs Long-term administration of leuprolide, goserelin and buserelin are useful in prostatic and breast cancers. They may be combined with tamoxifen in breast cancers.

Antiandrogen Flutamide is used in prostatic cancer.

RADIOACTIVE ISOTOPES

Some radioactive isotopes can be used in the treatment of certain specific cancers.

Radiophosphorus P32 is used in polycythemia vera. It is taken up by the bone where it emits β rays and has a half-life of about 14 days.

Strontium chloride emits β rays and has a longer $t_{1/2}$ in the bony metastases. It is used to alleviate pain in painful bony metastases.

Radio active iodine I¹³¹ is used in the treatment of thyroid cancers (See Page 344).

OTHER AGENTS

Several agents are used to beneficially influence the patients' response to treatment and to overcome some adverse effects. These have also been termed *biological response modifiers*. They are as follows:

1. *Haematopoietic growth factors* like erythropoietin and myeloid growth factors like GM-CSF, G-CSF, M-CSF and thrombopoietin (see Page 225) are used to treat bone marrow suppression.
2. Interferons (see Page 308) like interferon α are used in hairy cell leukaemia, Kaposi's sarcoma and condylomata acuminata.
3. Monoclonal antibodies are immunoglobulins that react specifically with antigens present on the cancer cells. Allergic reactions are common. *Trastuzumab* also enhances host immune responses and is useful in breast cancers. *Rituximab* attaches to antigens on the B cells causing lysis of these cells. It is used in B cell lymphomas.

General Principles in the Treatment of Cancers (Table 47.3)

Chemotherapy in cancers is generally palliative and suppressive. Chemotherapy is just one of the modes in the treatment of cancer. Other modes like radiotherapy and surgery are also employed. Combination of drugs is preferred for synergistic effect, to reduce adverse effects and to prevent rapid development of resistance. Drugs which do

not depress bone marrow are useful in combination regimens to avoid overlapping of adverse effects. With appropriate treatment, cure can now be achieved in a few cancers. Maintenance of good nutrition, treatment of anaemia, protection against infections, adequate relief of pain and anxiety and good emotional support—all go a long way in the appropriate management of this dreaded disease.

Table 47.3: Choice of drugs in some malignancies

<i>Malignancy</i>	<i>Preferred drugs</i>	
Acute lymphatic leukaemia	Vincristine + prednisolone Maintenance - Mercaptopurine/Methotrexate, Cyclophosphamide	
Acute myeloid leukaemia	Cytosine arabinoside + daunorubicin	
Chronic lymphatic leukaemia	Chlorambucil + Prednisolone	
Chronic myeloid leukaemia	Busulfan Imatinib; interferons	
Hodgkin's disease	M-Mechlorethamine O-Oncovin (Vincristine) P-Procarbazine P-Prednisolone - MOPP	Vinblastin Doxorubicin Dacarbazine Bleomycin
Non-Hodgkin's lymphoma	Cyclophosphamide + doxorubicin + vincristine + prednisolone	
Carcinoma of stomach	Fluorouracil + cisplatin	
Carcinoma of colon	Fluorouracil + irinotecan	
Multiple myeloma	Melphalan + Prednisolone	
Choriocarcinoma	Methotrexate	
Carcinoma of testis	Etoposide + bleomycin + cisplatin	
Osteogenic sarcoma	Methotrexate or doxorubicin, vincristine	
Wilms' tumour	Vincristine + actinomycin-D after surgery	
Carcinoma of the head and neck	Fluorouracil + cisplatin	
Carcinoma of lung	Cisplatin + paclitaxel	

Hypothalamus and Anterior Pituitary Hormones

The pituitary gland, under the influence of the hypothalamus secretes many hormones which either control the secretion of other glands or directly act on the target tissues. These are peptides and act by binding to specific receptors present on the target cells (Table 48.1).

Hypothalamic Hormones

Growth hormone releasing hormone (GHRH), (sermorelin) stimulates anterior pituitary to secrete growth hormone. Sermorelin (Table 48.2) is an analog of GHRH used in diagnostic tests of growth hormone deficiency (Table 48.3).

Somatostatin is growth hormone release-inhibiting hormone present in the hypothalamus, parts of the CNS, pancreas and in gastrointestinal tract. It inhibits the secretion of growth hormone, TSH, prolactin, insulin, glucagon and gastro the intestinal secretions. But it is very short-acting. *Octreotide* is the synthetic analog of somatostatin which is longer-acting and useful in acromegaly, some hormone secreting tumours and in bleeding oesophageal varices.

Thyrotrophin releasing hormone (TRH) secreted by the hypothalamus stimulates the release of TSH from the anterior pituitary. *Protirelin*

is a synthetic analog of TSH used in the diagnosis of thyroid disorders.

Corticotrophin releasing factor (CRF) releases ACTH and β -endorphins from the anterior pituitary. It is used in diagnostic tests in Cushing's disease.

Gonadotrophin-releasing hormone (GnRH, LHRH, Gonadorelin)—secreted in a pulsatile manner, regulates the secretion of gonadotrophins—FSH and LH. It is used in diagnostic tests in hypogonadism. Therapeutically pulsatile administration is used in infertility and delayed puberty. Continuous administration inhibits gonadotrophin secretion and is used in prostatic cancers. GnRH analogue *leuprolide* is more potent and is used for pharmacological orchiectomy/oophorectomy in prostatic cancer and some gynaecological conditions like uterine fibroids and endometriosis.

ANTERIOR PITUITARY HORMONES

Growth hormone (GH) a peptide, stimulates the growth of all organs except brain and eye. It increases the uptake of amino acids by the tissues, promotes protein synthesis and positive nitrogen balance. It causes lipolysis and reduces glucose uptake by skeletal muscles. It brings about linear growth. These

Table 48.1: Hormones secreted by the hypothalamus and anterior pituitary and their chief functions

<i>Hypothalamic hormone</i>	<i>Anterior pituitary hormone</i>	<i>Chief actions</i>
1. a. Growth hormone releasing hormone (GHRH) b. Growth hormone release-inhibiting hormone (somatostatin) (GHRH)	Growth hormone (GH) Inhibits GH release	Regulates growth
2. Corticotropin releasing factor (CRF)	Corticotrophin (ACTH)	Stimulates adrenal cortex to secrete glucocorticoids, mineralocorticoids and androgens
3. Thyrotropin-releasing hormone (TRH)	Thyroid-stimulating hormone (TSH) (Thyrotrophin)	Stimulates release of T ₃ and T ₄
4. Gonadotrophin releasing hormone (GnRH, somatostatin)	- Follicle stimulating hormone (FSH) - Luteinising hormone (LH) or (ICSH)	Stimulates growth of ovum and graafian follicle in the female and gametogenesis in the male Stimulates ovulation in females and regulates testosterone secretion in males
5. Prolactin-releasing factor	Prolactin (PRL)	Development of breast and lactation
6. Prolactin-release inhibiting factor	—	Inhibits prolactin-release
7. Melanocyte stimulating hormone - releasing factor	Melanocyte stimulating hormone	Promotes melanine synthesis causing darkening of skin; regulates feeding

Table 48.2: Analogs of hypothalamic and anterior pituitary hormones

<i>Hormones</i>	<i>Analogs</i>
GHRH	Sermorelin
Somatostatin	Octreotide
Thyrotrophin (TSH)	Protirelin
GnRH	Buserelin Leuprorelin Goserelin Nafarelin
ADH	Desmopressin Terlipressin Felypressin

anabolic actions are mediated by *somatomedins* or *insulin-like growth factors* (IGF) produced in the liver.

The secretion of growth hormone is regulated by GHRH and somatostatin (GHRH).

GH deficiency in children results in *dwarfism* while excessive production results in *gigantism* in children and *acromegaly* in adults.

Uses (Table 48.4)

- *GH deficiency* Replacement therapy with GH in deficient children brings about

Table 48.3: Uses of Hypothalamic hormones

<i>Hypothalamic hormone</i>	<i>Uses</i>
1. Sermorelin	Diagnosis of GH deficiency
2. Octreotide	Acromegaly, hormone secreting tumours, bleeding oesophageal varices.
3. TRH	Diagnosis of thyroid disorders
4. CRF	Diagnostic tests in Cushing's disease, tests of hypothalamic and pituitary function
5. GnRH (gonadorelin)	Diagnostic tests of hypogonadism
6. Leuprolide	Prostatic cancer, uterine fibroids

normal growth. It can also be used in GH deficient adults.

- *Other conditions* GH has been tried in chronic renal failure and in catabolic states – like severe burns and AIDS. It is liable for abuse in athletes to promote growth.

Corticotrophin (Adrenocorticotrophic hormone, ACTH) controls the synthesis and release of glucocorticoids, mineralo-corticoids, and androgens from the adrenal cortex (Fig. 50.1). It is used in the diagnosis of adrenocortical insufficiency.

Thyroid-stimulating hormone (TSH, Thyrotrophin) Thyrotrophin stimulates the production and secretion of thyroid hormones and thus regulates thyroid function. It is used to test thyroid function and to increase the uptake of radioactive iodine in thyroid carcinoma.

Gonadotrophins Follicle stimulating hormone (FSH) and luteinising hormone (LH)–produced by the anterior pituitary regulate gonadal function. They stimulate follicular development in women and also stimulate ovarian steroidogenesis (oestrogens and progesterone synthesis). In men they promote spermatogenesis.

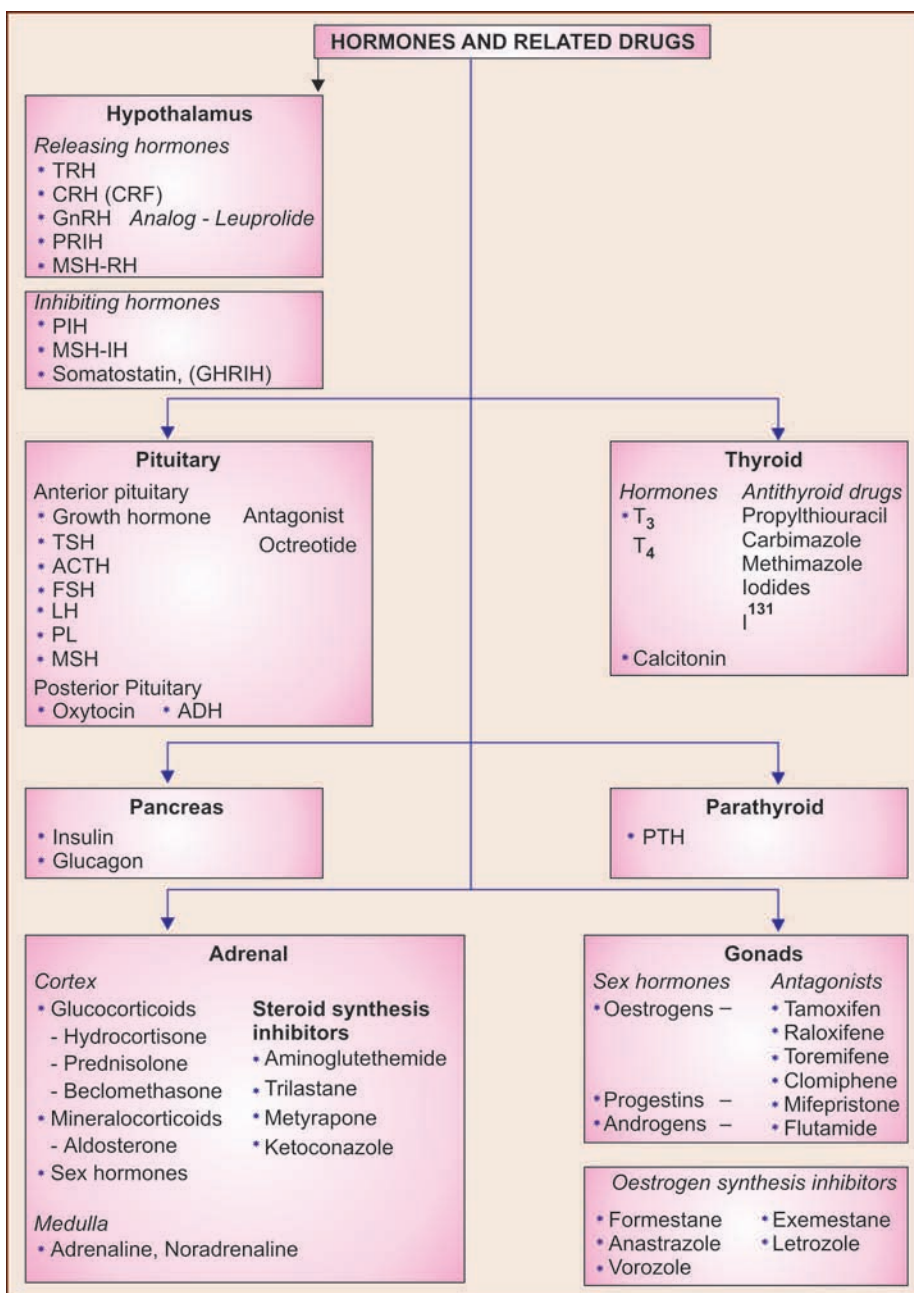
Uses Menotropins is the combination of FSH-LH obtained from the urine of postmenopausal women. It is used in:

1. Gonadotrophin deficiency in males.
2. Undescended testes.
3. Amenorrhoea and infertility.
4. *In vitro* fertilization - to time the ovulation.

Prolactin This peptide hormone promotes the growth and development of breast during pregnancy. It stimulates milk production along with other hormones like oestrogens

Table 48.4 : Uses of anterior pituitary hormones

<i>Anterior pituitary hormones</i>	<i>Uses</i>
1. Growth hormone	GH deficiency, Chronic renal failure, burns, Diagnosis of GH deficiency
2. Corticotrophin	Diagnosis of adrenocortical insufficiency
3. Thyrotrophin	To test thyroid function
4. Gonadotrophins	FSH-LH deficiency, undescended testes, amenorrhoea, infertility



Few examples have been given for each group

and progestins. Deficiency results in lactation failure while excess prolactin results in galactorrhoea.

Regulation of secretion—suckling is the principal stimulus for prolactin secretion. Suckling stimulates the release of prolactin-releasing factor from hypothalamus. Oestrogens and dopamine antagonists also stimulate prolactin-release. Prolactin is not used clinically.

Dopamine agonists like bromocriptine inhibit prolactin-release.

Bromocriptine is an ergot derivative with dopamine agonistic properties.

Bromocriptine is used

1. To suppress lactation and breast engorgement after delivery (like in still

birth) and following abortion. Bromocriptine stimulates the dopamine receptors in the pituitary to inhibit the release of prolactin.

2. In galactorrhoea—due to excess prolactin.
3. Prolactin secreting tumours or prolactinomas.
4. Parkinsonism—bromocriptine is used with levodopa.
5. Acromegaly—In normal subjects, dopamine agonists stimulate the release of growth hormone by the pituitary but in patients with acromegaly, they suppress growth hormone release by a paradoxical effect. Bromocriptine is therefore used in acromegaly. It also reduces prolactin release.

49

Thyroid Hormones and Antithyroid Drugs

THYROID HORMONES

Thyroxine (T_4) and triiodothyronine (T_3) are iodothyronine hormones secreted by the thyroid gland. The other hormone, calcitonin is secreted by the parafollicular cells (see page 375). T_4 is a less active precursor of T_3 .

Synthesis, Storage and Secretion The thyroid hormones are synthesized and stored in the thyroid follicles. The principle source of iodine is diet. The main steps involved in the synthesis of thyroid hormones are as follows: (Fig. 49.1)

1. **Uptake** of plasma iodide by thyroid cells by an active transport process with the help of sodium - iodide symporter.
2. **Oxidation** of iodide to I^+ (iodinium ions) by a thyroperoxidase enzyme with the help of hydrogen peroxide. These combine with tyrosine residues of thyroglobulin (TG) to form monoiodotyrosine (MIT) and diiodotyrosine (DIT).
3. **Coupling** Pairs of MIT and DIT are coupled to form T_3 (MIT+DIT) and T_4 (DIT+DIT) catalysed by the same peroxidase enzyme.
4. **Storage** TG containing iodinated tyrosine residues are stored in the follicles.
5. **Release** the hormones T_4 and T_3 are released into the circulation.

Regulation-The thyroid secretion is regulated by TSH secreted by the anterior pituitary and TRH from the hypothalamus (Fig. 49.2).

Normally about 70-90 mcg of T_4 and 15-30 mcg of T_3 are secreted daily. In the peripheral tissues, most of the secreted T_4 is converted to T_3 which is the active hormone. Both T_4 and T_3 are extensively bound to plasma proteins. The free hormone is metabolised in the liver and excreted in the bile. The $t_{1/2}$ of T_4 is 6-7 days and that of T_3 is 1-2 days. T_3 is 3-5 times more potent than T_4 and acts faster.

Actions Thyroid hormones are essential for normal growth, development, function and

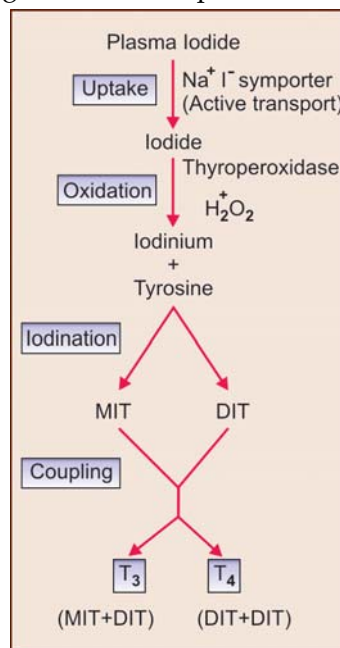


Fig. 49.1: Steps in thyroid hormone synthesis

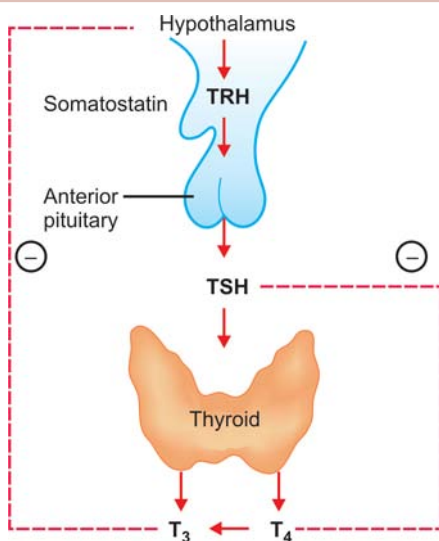


Fig. 49.2: Regulation of thyroid hormone secretion

maintenance of all body tissues. Congenital deficiency results in cretinism. Thyroid hormones have important metabolic functions – they increase metabolic rate, enhance carbohydrate and protein metabolism and stimulate lipolysis. They facilitate erythropoiesis, are essential for normal functioning of the CNS (mental retardation is seen in cretinism), skeletal muscles, cardiovascular system, reproductive system and gastrointestinal system (hypothyroid patients are constipated while hyperthyroid have diarrhoea).

Mechanism of action Thyroid hormones act on specific receptors. Thyroid receptors are nuclear receptors like the steroid receptors. T₃ enters into the cells, bind to the receptor and the T₃ - receptor complex moves to the nucleus where it binds to DNA, activates gene transcription and regulates protein synthesis (see Fig. 50.2 Page 349).

Uses Both thyroxine and triiodothyronine are available. Levothyroxine is synthetic T₄ and leothyronine is synthetic T₃ and are given orally.

1. Replacement therapy

- *Cretinism*, may be sporadic or endemic. Congenital absence of thyroid or defective thyroid hormone synthesis cause sporadic cretinism. Extreme deficiency of iodine can also result in endemic cretinism. Treatment should be started immediately to avoid mental retardation. Early detection and treatment produce dramatic results with normal physical and mental development. Levothyroxine (10-15 mcg/kg/day orally) is started and treatment monitored. Replacement should be continued lifelong.
 - *Hypothyroidism in adults* results from decreased thyroid activity and can be reversed by appropriate treatment. Treatment is started with levothyroxine 50 mcg daily and increased gradually every 2-3 weeks, depending on the plasma TSH levels.
 - *Myxoedema coma* is a medical emergency. IV thyroxine 500 mcg or liothyronine 100 mcg should be given with prophylactic corticosteroids to avoid adrenal insufficiency.
2. *Non-toxic goitre* T₄ suppresses TSH production and the goitre regresses.
 3. *Thyroid carcinoma* T₄ induces temporary remission. It is used after surgery.
 4. *Miscellaneous* Thyroxine is tried in refractory anaemias, infertility and non-healing ulcers.

HYPERTHYROIDISM AND ANTITHYROID DRUGS

Hyperthyroidism is due to an excess of circulating thyroid hormones and could be due to various causes. Graves' disease, an autoimmune disorder, is the most common cause. It is characterised by hyperthyroidism, diffuse goitre and IgG antibodies that activate TSH receptors. Antithyroid drugs

may act by interfering with the synthesis, release or actions of thyroid hormones.

Drugs Used in Hyperthyroidism

1. Antithyroid drugs

Thioureylenes -
Propylthiouracil,
Methimazole,
Carbimazole.

2. Iodine, Iodides, Radioactive iodine.

Thioureylenes are thionamides and include propylthiouracil, methimazole and carbimazole.

Actions Thioureylenes reduce the synthesis of thyroid hormones by inhibiting iodination of tyrosine residues and coupling of iodotyrosine residues. They bring about these effects by inhibiting the peroxidase enzyme. Propylthiouracil also inhibits peripheral conversion of T_4 to T_3 . T_3 and T_4 levels fall. Large doses may stimulate release of TSH resulting in thyroid enlargement. Over 3-4 weeks of treatment, the signs and symptoms of hyperthyroidism subside. Propylthiouracil is faster acting while

carbimazole is longer acting. Carbimazole is a prodrug of methimazole.

Pharmacokinetics Thioureylenes are effective orally; about 75% propylthiouracil is firmly bound to plasma proteins - hence very little crosses the placenta and a negligible fraction reaches the milk; but carbimazole and methimazole cross the placenta and are secreted in the milk (Table 49.1). Thioureylenes are concentrated in the thyroid. They are metabolised in the liver.

Adverse effects are allergic reactions, jaundice and headache. Agranulocytosis is a rare but serious adverse effect which occurs in about 0.1% of patients. It is reversible on stopping the antithyroid drug but patient should be monitored with frequent WBC counts.

Uses

Hyperthyroidism - antithyroid drugs are used in hyperthyroidism.

- Graves' disease* or diffuse toxic goitre needs long-term (1-15 yr) treatment with antithyroid drugs. Patients are usually euthyroid after 8-12 weeks of treatment. Smaller maintenance doses (Table 49.2) are then sufficient.

Table 49.1: Compare and contrast propylthiouracil and methimazole carbimazole

Features	Propylthiouracil	Methimazole
Onset of action	Faster acting	Slower acting
$t_{1/2}$	1-2 hours	6 hours
Additional action	Prevents peripheral conversion of $T_4 \rightarrow T_3$	No such effect
Protein binding	75%, Firmly protein bound	Nil
Placental transfer	Negligible	Significant
Secretion in milk	Negligible	Significant
Pregnancy	Preferred	Not Preferred
Lactating mothers	Drug of choice	Not used
Dose frequency	t.i.d.- q.i.d.	o.d.- b.i.d.
(Carbimazole is a prodrug, converted to methimazole in the body)		

- b. *Toxic nodular goitre* Antithyroid drugs are used as alternatives when surgery cannot be done as in the elderly patients.
- c. *Preoperatively* – hyperthyroid patients are made euthyroid with antithyroid drugs and then operated.
- d. Hyperthyroidism in pregnancy - is rare but when severe, requires treatment. Propylthiouracil is the preferred drug as it poorly crosses the placental barrier. It is also preferred in thyrotoxicosis in lactating mothers as only a negligible amount of propylthiouracil is secreted in the milk.
- e. *Thyroid storm* or thyrotoxic crisis is sudden, severe exacerbation of thyrotoxicosis and can be life threatening. It is precipitated by factors like stress, infections, trauma, surgery, etc. Symptoms include fever, tachycardia, nausea, vomiting, diarrhea, confusion, restlessness and may lead on to coma and death. Propylthiouracil, oral/rectal potassium iodide, IV hydrocortisone, tepid sponging, sedation, IV fluids and supportive therapy are needed immediately. Propranolol may be used to rapidly control the symptoms. It also impairs the conversion of T_4 to T_3 which may add to the beneficial effect.

Iodides inhibit the release of thyroid hormones and when given in thyrotoxic patients the symptoms subside in 1-2 days. The gland becomes firm, less vascular and shrinks in size over a period of 10-14 days. These effects are transient and decrease after 15 days. Iodides are administered orally as Lugol's iodine or as potassium iodide solution - 3 drops 3 times a day.

Drugs that influence thyroid function

Amiodarone	Phenytoin
Sulfonamides	Carbamazepine
Lithium	Sodium nitroprusside

Lugol's iodine is 5% iodine in 10% potassium iodide. Iodine is converted into iodides in the intestine which is then absorbed.

Adverse effects include allergic reactions like skin rashes, conjunctivitis, swelling of the lips and salivary glands, fever and lymphadenopathy. Chronic overdose can cause *iodism* with metallic taste, excessive salivation, lacrimation, burning sensation in the oral cavity and throat, running nose, sore throat, cough, headache and rashes.

Uses

1. *Preoperative preparation for thyroidectomy* Iodine is started just 10 days prior to surgery to make the thyroid gland firm and less vascular.
2. *Thyroid storm* Iodides act rapidly to reduce the release of thyroid hormones.
3. *Prophylaxis* Iodide or iodate is added to common salt to prevent endemic goitre.
4. *Antiseptic* see Page 378.
5. *Expectorant* Used in cough.

Radioactive iodine ^{131}I given orally as a solution is rapidly absorbed and is concentrated by the thyroid in the follicles. It emits both γ and β rays. The γ rays pass through the tissue while β particles penetrate only 0.5 to 2 mm of the tissue due to which it destroys only the thyroid tissue without damaging the

Table 49.2 : Dosage of antithyroid drugs

Drug	Daily dose
Carbimazole	Start with 15-45 mg Maintenance 5-10 mg
Methimazole	Start 15- 30 mg Maintenance 5-15 mg
Propylthiouracil	Start 150-300 mg Maintenance 40-100 mg
Lugol's Iodine (5% iodine in 10% potassium iodide solution)	5-15 drops

surrounding structures. Iodides also inhibit the synthesis of thyroid hormone for 1-2 days (known as Wolff-Chaikoff effect). ^{131}I has a half-life of 8 days but the radioactivity is present upto 2 months. It is given as a single dose; clinically the effect is seen after 1-2 months.

Radioactive Iodine (3–10 m curie) is used in the treatment of hyperthyroidism and in thyroid carcinoma. Small dose is used for diagnostic purpose in thyroid function tests.

Advantages of ^{131}I over thyroidectomy are that

- (i) administration is simple,
- (ii) convenient;
- (iii) surgery and its associated risks can be avoided.
- (iv) less expensive when compared to surgery.

The disadvantages are:

- (i) the long time (3 months) taken for maximum response
- (ii) the risk of hypothyroidism which may develop after a few months or years.

The patient should be followed up for the symptoms of hypothyroidism and replacement therapy with thyroid hormones should be promptly given.

β -adrenergic blockers Many of the symptoms of hyperthyroidism are of sympathetic overactivity as there is increased tissue sensitivity to catecholamines in hyperthyroidism. β adrenergic blockers like propranolol relieve symptoms like palpitation, tremors, nervousness, sweating and myopathy. They only afford symptomatic relief and are used as adjuvants in hyperthyroidism and thyrotoxic crisis.

Ionic inhibitors interfere with the concentration of iodine by the thyroid gland. Thiocyanate and perchlorate inhibit the organification of iodine but are not used now due to the adverse effects. Food items like cabbage; cigarette smoking and drugs like sodium nitroprusside, increase the concentration of thiocyanate in the blood and may result in hypothyroidism.

Corticosteroids

Corticosteroids are hormones produced in the cortex of the adrenal gland. They are glucocorticoids, mineralocorticoids and a small amount of androgens. Cortisol is the major glucocorticoid while aldosterone is the major mineralocorticoid. The secretions of the adrenal cortex are under the control of ACTH secreted by the anterior pituitary and this is in turn regulated by CRF and plasma corticosterone levels (Fig. 50.1). This is termed hypothalamic-pituitary-adrenal axis.

STRUCTURE AND SYNTHESIS

The corticosteroids have a cyclopentano-perhydrophenanthrene (steroid) ring. They are synthesized in the adrenal cortex from cholesterol under the influence of ACTH.

Everyday about 10-20 mg of hydrocortisone (maximum in the early morning) and 0.125 mg of aldosterone are secreted. They are also released in response to stress.

ACTIONS

Glucocorticoid Actions

1. Metabolic effects

Carbohydrate, protein and fat metabolism—Glucocorticoids promote gluconeogenesis and glycogen deposition in the liver and inhibit peripheral utilization of glucose resulting in increased blood glucose levels.

They enhance protein breakdown and nitrogen is excreted leading to negative nitrogen balance. Glucocorticoids are catabolic hormones.

Glucocorticoids promote lipolysis and redistribution of fat takes place—fat is mobilised from extremities and deposited over the face, neck and shoulder and this fat deposition in excess glucocorticoid activity

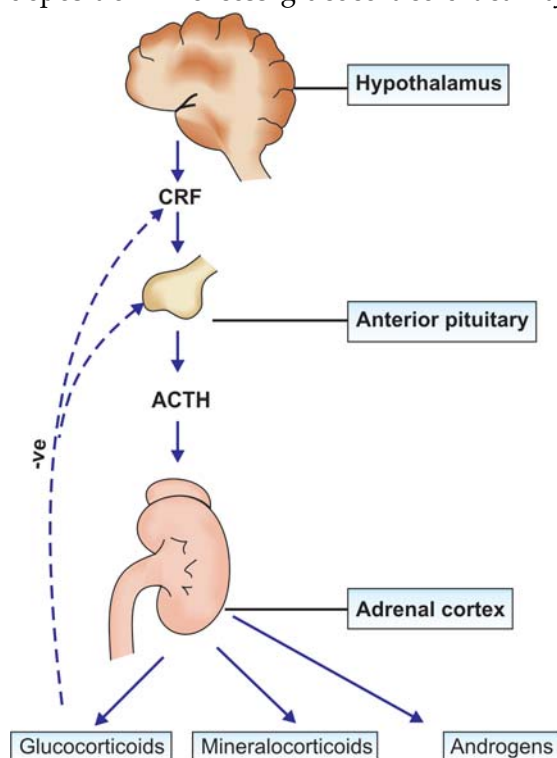


Fig. 50.1: Hypothalamic-pituitary-adrenal axis regulation of synthesis and secretion of adrenal corticosteroids

is described as 'moon face', 'fish mouth' and 'buffalo hump'.

2. *Anti-inflammatory and immunosuppressive effects* Glucocorticoids suppress the development of inflammatory response to all types of stimuli like chemical, mechanical and immunological stimuli. They inhibit both early and late manifestations of inflammation. Inhibition of late response like capillary proliferation, collagen deposition, fibroblastic activity and scar formation may delay wound healing. They inhibit migration and depress the function of the leucocytes and macrophages and inhibit the release of chemical mediators. The ability of these cells to respond to antigens is decreased. Glucocorticoids - even a single dose bring about a decrease in the number of WBCs - lymphocytes, monocytes, eosinophils and basophils decline. In addition glucocorticoids also induce the synthesis of a protein - lipocortin, which inhibits phospholipase A₂ thereby decreasing the production of prostaglandins and leukotrienes.

Glucocorticoids thus suppress cell-mediated immunity, prevent manifestations of allergy and prevent homograft rejection. Large doses also inhibit antibody production.

3. *Other actions*

- Glucocorticoids reduce capillary permeability, thereby reducing fluid exudation and maintain the tone of arterioles. They have a positive inotropic effect on the heart. Prolonged use can cause hypertension.
- They are essential for normal muscular activity.
- They are required for normal functioning of the central nervous system. Deficiency results in apathy and depression while large doses result in restlessness, anxiety and sometimes psychosis.

- GIT-Glucocorticoids enhance the secretion of gastric acid and pepsin in the stomach.
- Calcium metabolism-Glucocorticoids inhibit absorption and enhance the renal excretion of calcium—they antagonise the effect of vitamin D on calcium absorption. Bone resorption takes place.
- Formed elements of blood-glucocorticoids have a lympholytic effect which is very prominent in lymphomas; but they increase the number of platelets and RBCs.
- They are essential for maintaining normal GFR.

4. *Mineralocorticoid action* Glucocorticoids also have a weak mineralocorticoid action—cause some salt and water retention and potassium excretion. Some synthetic glucocorticoids are devoid of this activity.

Mechanism of Action

Corticosteroids enter the cells by simple diffusion, bind to specific receptors in the cytoplasm (Fig. 50.2) and activate them. The drug-receptor complex is then transported into the nucleus where it binds to specific sites on DNA and induce the synthesis of specific mRNA. By this they regulate the synthesis of new proteins that bring about the hormone effects.

PHARMACOKINETICS

Most glucocorticoids are well-absorbed orally. Hydrocortisone undergoes high first pass metabolism. It is 95% bound to plasma proteins—corticosteroid binding globulin (CBG) or transcortin. Glucocorticoids are metabolised in the liver by oxidation and reduction followed by conjugation. Metabolites are excreted by the kidneys. The

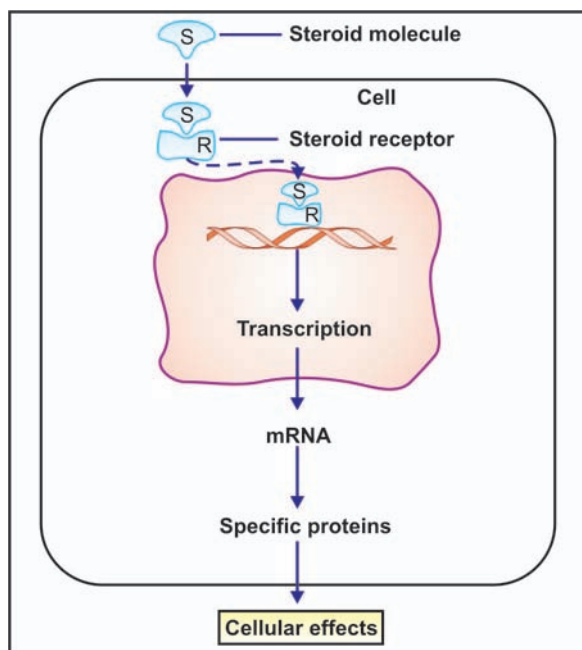


Fig. 50.2: Mechanism of action of corticosteroids

$t_{1/2}$ varies with each agent and we have short, intermediate and long-acting agents (Table 50.1).

Preparations Glucocorticoids are given by many routes - orally, parenterally, topically, by inhalation and nasal spray. They may also be injected intra-articularly. The synthetic analogs are more potent than hydrocortisone and have less or no mineralocorticoid activity (Table 50.2).

- Hydrocortisone, the chief natural glucocorticoid is used orally and parenterally; in emergencies it is used intravenously.
- Prednisolone has potent glucocorticoid with mild mineralocorticoid activity. It is the most commonly used glucocorticoid.
- Prednisone is a prodrug converted to prednisolone in the liver.
- Methylprednisolone is similar to prednisolone and is used as retention enema and for high dose pulse therapy.
- Triamcinolone, dexamethasone, betamethasone have no mineralocorticoid activity and have selective, potent glucocorticoid effects.

Table 50.1: Relative potency of some corticosteroids

Drug	Glucocorticoid activity	Mineralocorticoid activity	Equivalent dose
<i>Short-acting (8-12 hr)</i>			
Hydrocortisone	1	1	20 mg
Cortisone	0.8	0.8	25 mg
<i>Intermediate-acting (18-36 hr)</i>			
Prednisolone	4	0.8	5 mg
Methylprednisolone	5	0.5	4 mg
Triamcinolone	5	0	4 mg
Fludrocortisone	10	125	2 mg
<i>Long-acting (36-54 hr)</i>			
Paramethasone	10	0	2 mg
Dexamethasone	25	0	0.75 mg
Betamethasone	30	0	0.6 mg

Table 50.2: Preparations and dose of some commonly used glucocorticoids

Glucocorticoid	Trade name	Dosage form	Daily dose
Hydrocortisone hemisuccinate	EFCORLIN	10 mg tablet 50 mg/ml inj IM, IV Also available for retention enema, IA inj and topical use	30-100 mg
Prednisolone	WYSOLONE	5,10, 20 mg tab 20 mg/ml inj pediatric and topical preparations also available	5-60 mg oral 10-40 mg IM
Methylprednisolone acetate	SOLVMEDROL	4 mg tab 20 mg/ml inj Retention enema	4-32 mg
Triamcinolone	KENACORT	4 mg tab 10 mg/ml inj 5- 40 mg inj IM/IA	4-20 mg
Dexamethasone	DEXONA	0.5 mg tab 4 mg/ml inj 0.1% ointment	0.5-5 mg oral 4-20 mg IV/IM
Betamethasone	BETNESOL	0.5 mg tab 4 mg/ml inj 0.025% ointment	0.5-5 mg oral 4-20 mg IM/IV
Topical : IM = intramuscular, IV = intravenous, IA = intra-articular			

- *Topical Preparations*

Several glucocorticoids like hydrocortisone, dexamethasone and betamethasone are available for topical use as creams, ointments, nasal and eye drops. Some of them also contain antibiotics.

- Beclomethasone, budesonide, fluticasone are available for inhalation.

Adverse Effects of Glucocorticoids

Adverse effects of glucocorticoids (Fig. 50.4) are dependent on dose, duration of therapy and the relative potency of additional mineralocorticoid effects. Whenever possible, they should be used topically to avoid systemic effects. Single doses are harmless while short courses are well-tolerated. Prolonged use is associated with toxicity. Adverse effects include:

1. *Cushing's syndrome* with characteristic appearance of moon face, supraclavicular hump (buffalo hump), truncal obesity, muscle wasting, thinning of the limbs and skin, easy bruising, purple striae and acne.
2. *Hyperglycaemia* and sometimes diabetes mellitus may be precipitated.
3. *Susceptibility to infections* is increased and the severity of any infection may be more because of immunosuppression. Opportunistic infections may occur. Previously dormant tuberculosis may become active.
4. *Osteoporosis* especially of the vertebrae is more common in the elderly.
5. *Avascular necrosis* of the bone due to restriction of blood flow through bone capillaries may cause joint pain, stiffness and restriction of movement. Head of the femur, humerus and distal part of femur may be

affected. Growth in children may be suppressed.

6. *Peptic ulceration* may sometimes occur on prolonged therapy especially when other ulcerogenic drugs (e.g. NSAIDs) are used concurrently.

7. *Mental disturbances* Alterations in behaviour can occur with high doses of steroids. Symptoms may range from insomnia, anxiety, nervousness, mood changes, euphoria, psychosis or depression.

8. *Cataract* and *glaucoma* may follow long-term use of glucocorticoids even as eye drops. Patients receiving long-term steroids should undergo eye examinations for these.

9. *Delayed wound healing* Steroids may delay wound healing.

10. *Other effects* include raised intracranial pressure, convulsions, hypercoagulability of the blood and menstrual disorders.

11. *HPA axis suppression* depends on the dose, duration and time of administration. After prolonged steroid therapy, adrenal cortex gradually atrophies due to feedback inhibition. If steroid administration is suddenly stopped, acute adrenal insufficiency results. Hence after prolonged administration, steroids should be tapered before withdrawal to allow HPA axis to recover. Prior to surgery or general anaesthesia, it is

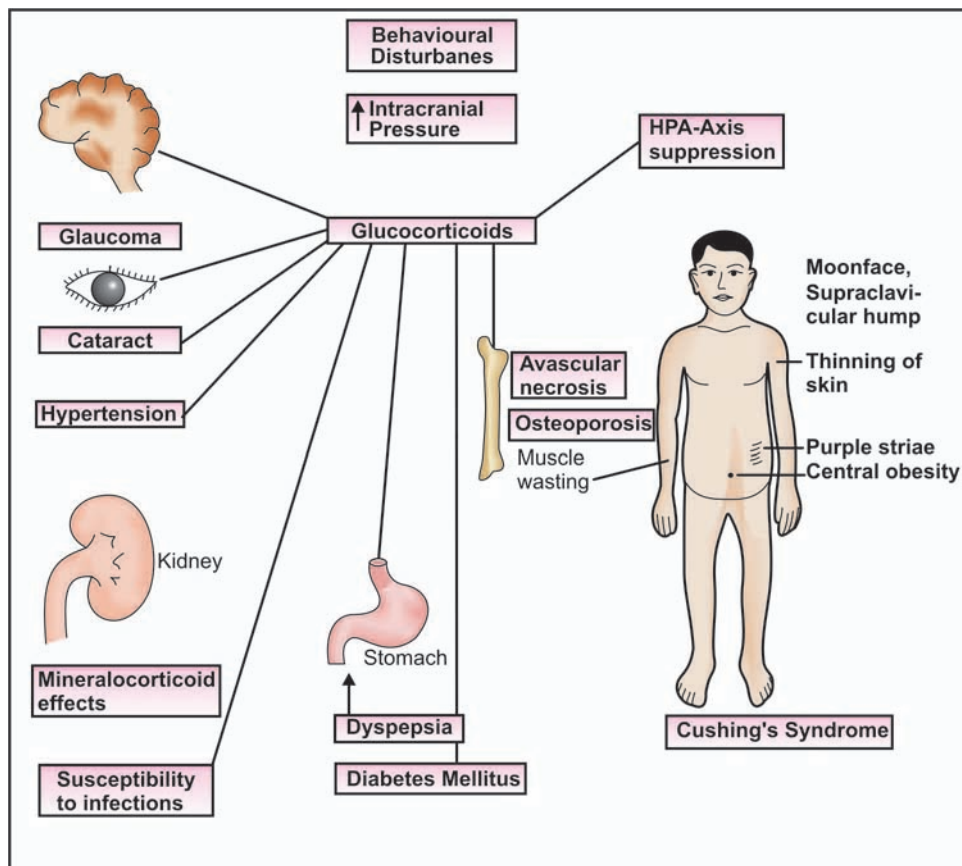


Fig. 50.3: Adverse effects of glucocorticoids

advisable to elicit proper drug history. If the patient has received long-term steroids within previous six months, it is prudent to administer prophylactic hydrocortisone to avoid shock. Two weeks of use of > 20 mg hydrocortisone/day needs tapering of the dose.

In order to minimize HPA axis suppression, *lowest effective dose* of a glucocorticoid for the *shortest possible period* should be used. The drug should be given in a *single morning dose*. Administration on *alternate days* is found to be associated with least/no HPA axis suppression and whenever possible this measure should be followed, especially when long-term steroids are needed.

12. *Mineralocorticoid effects* including salt and water retention, oedema, hypokalaemia and hypertension are rare with selective glucocorticoids.

Uses

I. Replacement therapy

A. *Acute adrenal insufficiency* is an emergency condition that could be precipitated by an infection or sudden withdrawal of steroids. Symptoms include nausea, vomiting, weakness, hypotension, dehydration, hyponatremia and hyperkalemia. Intravenous hydrocortisone hemisuccinate 100 mg

bolus followed by infusion is given immediately.

B. *Chronic adrenal insufficiency* (Addison's disease). Oral hydrocortisone 20-40 mg daily is given. Some patients may need additional fludrocortisone (a mineralocorticoid).

C. *Congenital adrenal hyperplasia* is characterised by impaired synthesis of corticosteroids due to deficiency of some enzymes involved in synthesis. As a result ACTH levels rise resulting in adrenal hyperplasia. Hydrocortisone and if required mineralocorticoids are given daily.

II. Pharmacotherapy

Glucocorticoids have been used in a variety of nonendocrine conditions where they are used for symptomatic relief, but may even be life saving.

1. *Rheumatoid arthritis* In progressive disease steroids are given with NSAIDs. If 1-2 joints are involved, intra-articular injections are preferred.

2. *Osteoarthritis* Steroids are given as intra-articular injections with strict aseptic precautions. A minimum of 3 months interval should be given between two injections of steroids into the joint. Repeated injections can result in joint destruction.

3. *Rheumatic carditis* Severely ill-patients with fever and not responding adequately to NSAIDs require glucocorticoids.

Table 50.3: Compare and contrast hydrocortisone and dexamethasone

Features	Hydrocortisone	Dexamethasone
Source	Natural	Synthetic
Mineralocorticoid activity	Present	Absent
Potency	Less potent	More potent
Equivalent dose	20 mg	0.75 mg
Plasma t _{1/2}	8-12 hrs	36-54 hrs
Duration of action	Short	Long
Production in the body	Endogenous	Not produced (Exogenous)

4. *Acute gout* When treatment with NSAIDs have not been successful, prednisolone is used as an adjuvant.

5. *Allergic diseases* like angioneurotic edema, hay fever, serum sickness, contact dermatitis, urticaria, drug reactions and anaphylaxis—steroids are indicated. Steroids are slow acting and in less severe cases, antihistamines should be preferred.

6. *Bronchial asthma*

- Acute exacerbations – a short course of prednisolone
- Status asthmaticus – intravenous hydrocortisone hemisuccinate 100-200 mg repeated after 8 hrs 40-60 mg per day.
- Chronic asthma—Inhalational steroids are used and in more severe cases low dose oral prednisolone is indicated. COPD— exacerbation may be treated with short course of prednisolone.

7. *Collagen diseases* like polyarthritis nodosa, lupus erythematosus, polymyositis, Wegener's granulomatosis and other rheumatoid disorders respond to glucocorticoids. Glucocorticoids are the first-line drugs. Prednisolone is given for 6 weeks and tapered over another 6 weeks.

8. *Eye diseases* Allergic conjunctivitis, uveitis, optic neuritis and other inflammatory conditions are treated with steroid eye drops. Long-term steroids administration can increase IOP which should be monitored. In ocular infections, steroids are contraindicated.

9. *Renal diseases* like nephrotic syndrome are treated with steroids. Glucocorticoids are the first line drugs.

10. *Skin diseases* Atopic dermatitis, seborrhoeic dermatitis, inflammatory dermatoses and other local skin conditions are treated with topical steroids. Systemic steroids are *life saving* in pemphigus.

11. *Gastrointestinal diseases* Mild inflammatory bowel diseases like ulcerative colitis are treated with steroid retention enema while severe cases need oral prednisolone.

12. *Liver diseases* Steroids are useful in conditions like autoimmune chronic active hepatitis and alcoholic hepatitis.

13. *Haematologic disorders* like purpura and haemolytic anaemia having immunological aetiology respond to steroids.

14. *Cerebral oedema* Large doses of dexamethasone reduces cerebral oedema occurring in some malignancies.

15. *Malignancies* Because of their lympholytic effects, steroids are used in the treatment of acute lymphocytic leukaemia and lymphomas. Steroids are also used for rapid symptomatic relief in other malignancies like breast cancer.

16. *Lung diseases* Apart from bronchial asthma, steroids are used in other diseases like aspiration pneumonia and prevention of infant respiratory distress syndrome.

17. *Organ transplantation* For prevention and treatment of graft rejection, high doses of prednisolone are started at the time of surgery with immunosuppressive agents.

18. *Others* - Glucocorticoids are useful in

- Sarcoidosis to induce remission.
- *Pneumocystis carinii pneumonia* is common in patients with AIDS - Glucocorticoids reduce the risk of respiratory failure and decrease mortality.

Table 50.4: Contraindications to glucocorticoid therapy

Steroids should be used with caution in:

- | | |
|--|-------------------|
| 1. Peptic ulcer | 6. Osteoporosis |
| 2. Hypertension | 7. Psychoses |
| 3. Infections | 8. Epilepsy |
| 4. Diabetes mellitus | 9. CCF |
| 5. Ocular infections particularly viral infections | 10. Glaucoma |
| | 11. Renal failure |

- In haemolytic anaemia glucocorticoids reduce the autoimmune destruction of erythrocytes.

Contraindications—see table 50.4.

MINERALOCORTICIDS

The most important natural mineralocorticoid is aldosterone synthesized in zona glomerulosa of the adrenal cortex. Small amounts of desoxycorticosterone is also released.

Actions Mineralocorticoids promote sodium and water retention by distal renal tubules with loss of potassium.

Adverse effects include weight gain, oedema, hypertension and hypokalaemia.

Fludrocortisone has predominantly mineralocorticoid properties and is used for replacement therapy in aldosterone deficiency as in Addison's disease. Although aldosterone is the principal natural mineralocorticoid, it is not used therapeutically since it is not effective orally.

INHIBITORS OF ADRENAL STEROIDS SYNTHESIS

Metirapone, trilastane, aminoglutethimide and ketoconazole These drugs inhibit the synthesis of adrenal steroids by inhibiting certain enzymes involved in steroid synthesis. They are used in Cushing's syndrome and some prostatic and breast cancers.

Steroids and Dentistry

Glucocorticoids are one of the most widely used drugs. When a patient on glucocorticoids, especially on long-term steroids requires a dental procedure, adequate precautions are to be taken.

(a) Patients on steroids are more susceptible to infections. Antibiotic coverage may be needed depending on the procedure

(b) If the patient is on steroids, it should be continued because if steroids are suddenly stopped, the patient may go into acute adrenal insufficiency (due to HPA axis suppression) particularly following major procedures. Infact patients on long-term glucocorticoids may require an additional dose of the steroid to manage the stress.

(c) Long-term administration of glucocorticoids may delay wound healing.

(d) If a patient on glucocorticoids, undergoes a dental procedure and requires NSAIDs for analgesia, care should be taken to use the ones which do not produce much gastric irritation - paracetamol (400-600 mg) or ibuprofen may be given. Both NSAIDs and glucocorticoids can produce gastric irritation and when given together it can be severe.

(e) Therapeutic use of steroids in dental procedures is not very common. Severe inflammation may rarely require steroids in addition to NSAIDs.

51

Oestrogens, Progestins and Hormonal Contraceptives

OESTROGENS

The oestrogens are produced by the ovaries, placenta and in small amounts by the adrenals and testes. The major oestrogens are oestradiol, oestrone and oestriol. oestradiol is converted to oestrone and oestriol by the liver and other tissues.

Natural oestrogens Oestrogens, oestradiol, oestrone, oestriol.

Synthetic oestrogens Ethinyl oestradiol, stilboestrol, mestranol.

Estrogen receptors are of two types—ER α and ER β .

Distribution—

ER α —Female reproduction tract, breast, blood vessels and hypothalamus.

ER β —Ovaries and prostate.

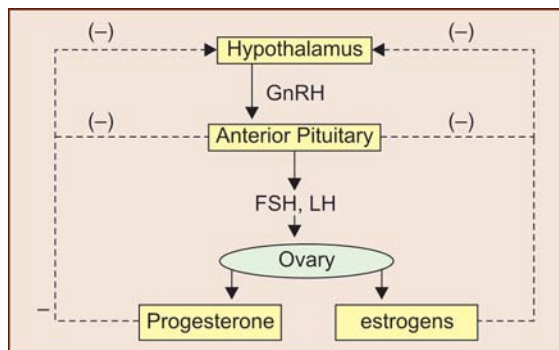


Fig. 51.1: Regulation of secretion of gonadal hormones

Actions Estrogens are required for—

1. the normal maturation of the female reproductive tract.
2. development of secondary sexual characters in the female.
3. stimulation of preovulatory endometrium.
4. metabolic effects—oestrogens inhibit the resorption of bone and maintain the bone mass. They promote the fusion of epiphyses.
5. Estrogens are important for the maintenance of normal structure of the skin and blood vessels in women.
6. oestrogens decrease plasma LDL cholesterol and raise HDL cholesterol and triglycerides.
7. effect on blood coagulation—oestrogens enhance the coagulability of the blood.

Pharmacokinetics Natural oestrogens are metabolised rapidly in the gut—hence are not effective orally; they have a short $t_{1/2}$. They are largely bound to plasma proteins. Synthetic oestrogens are orally effective and are long-acting.

Adverse effects Nausea, breast tenderness, migraine headaches, hyperpigmentation, hypertension and cholestasis may be seen. In men gynaecomastia and feminization can occur.

Cancers Increased incidence of endometrial and breast cancers are reported on long-term oestrogen therapy.

Teratogenic—When given to a pregnant lady oestrogens may cause:

- In female child—increased risk of vaginal and cervical cancers
- In male child—genital abnormalities.

Uses

1. Replacement therapy

- (a) In primary hypogonadism—Oestrogen started at 11-13 years of age stimulates the development of secondary sexual characters and menstruation.
 - (b) Postmenopausal syndrome—Due to decreased oestrogen production at menopause, hot flushes, anxiety, fatigue, sweating, muscle and joints pain are common (Post menopausal syndrome). Other longer-lasting changes including osteoporosis, genital atrophy, skin changes, increased risk of cardiovascular disease and psychological disturbances may be seen. Oestrogens given in low doses as hormone replacement therapy (HRT) are highly effective in reversing most of the changes.
2. *Senile vaginitis* is common in elderly women due to reduced oestrogen synthesis by the ovary—oestrogen cream is used topically.
 3. *Osteoporosis* In postmenopausal osteoporosis, oestrogens restore calcium balance and need to be given for a long time.
 4. *Oral contraceptives* Oestrogens are used (See Page 375) with progestins.
 5. *Dysmenorrhoea* oestrogens combined with progestins suppress ovulation and such anovulatory cycles are painless. Oestrogens are used only in severe dysmenorrhoea.

6. *Dysfunctional uterine bleeding* oestrogens are used as adjuvants to progesterone.

7. *Carcinoma prostate* is an androgen dependent tumour. Oestrogens antagonise the action of androgens, suppress androgen production and are useful for palliative therapy.

Contraindications Oestrogen dependent tumours, liver disease, thromboembolic disorders.

Selective oestrogen receptor modulators (SERMs) and anti-oestrogens.

Tamoxifen

Tamoxifen was earlier considered to be an oestrogen antagonist. But now it is understood that it acts as an agonist, antagonist or partial agonist depending on the site. *Raloxifene* and *toremifene* have actions similar to tamoxifen and are all termed selective oestrogen receptor modulators (SERMs). SERMs have tissue-selective oestrogenic activities. i.e.,

- they act as agonists at bone, lipid, brain and liver.
- antagonists at breast, pituitary and endometrium;
- partial agonist at genitourinary epithelium, in bone remodeling and cholesterol metabolism.

Tamoxifen By its tissue selective activity on the oestrogen receptor, tamoxifen:

- inhibits the proliferation of tumour cells in the breast.
- stimulates the proliferation of the endometrium.
- reduces bone resorption.
- decreases total cholesterol

Side effects include hot flushes, nausea, vomiting, vaginal dryness, cataract and skin rashes. Tamoxifen increases the risk of endometrial cancer and thromboembolism

Uses Breast cancer—Tamoxifen is used in the palliation of advanced breast cancer in postmenopausal women with oestrogen receptor positive tumours.

Raloxifene acts as an oestrogen receptor agonist in the bone. In women with postmenopausal osteoporosis, raloxifene has antiresorptive effects on the bone. It reduces bone loss and may even help to gain bone mass. Raloxifene also lowers LDL. It acts as an oestrogen antagonist in the breast due to which it reduces the incidence of breast cancer. Raloxifene does not stimulate the uterine endometrial proliferation.

Adverse effects include hot flushes, leg cramps and an increased risk of deep vein thrombosis and pulmonary embolism.

Raloxifene is indicated for the prevention of postmenopausal osteoporosis.

Toremifene has actions similar to tamoxifen and is indicated in the treatment of metastatic breast cancer in postmenopausal women.

Clomiphene Citrate

Clomiphene citrate binds to the oestrogen receptors and acts as a competitive inhibitor of endogenous oestrogens. Like tamoxifen, it is also a partial agonist. Clomiphene opposes the negative feedback of endogenous oestrogens on the hypothalamo-pituitary axis resulting in increased gonadotrophin secretion and thereby induces ovulation.

Side effects include ovarian hyperstimulation resulting in multiple pregnancy, ovarian cysts, hot flushes, headache and skin rashes.

Uses

1. *Infertility* Clomiphene citrate is used in infertility due to ovarian disorders. It is given orally, 50 mg daily for 5 days starting from 5th day of the cycle; course is repeated till ovulation occurs

2. *In vitro fertilization* Clomiphene induced ovulation is also useful in *in vitro* fertilization.

Oestrogen Synthesis Inhibitors

Aromatase inhibitors like formestane, exemestane, anastrozole, letrozole and vorazole block the production of oestrogens and are used in the treatment of breast cancer.

PROGESTINS

Progesterone is the natural progestin synthesized in the ovary and placenta. It is also synthesized by the testis and adrenals where it acts as a precursor of various steroid hormones (see under corticosteroids).

	<i>Progestins</i>
<i>Natural</i>	Progesterone
<i>Synthetic</i>	Medroxyprogesterone acetate
	Allylestrenol
	Megestrol
	Levonorgestrel
	Norethisterone acetate
	Lynestrenol
	Norgestimate

Actions

1. *Uterus* The secretory changes in the endometrium like increased tortuosity of the glands are due to progesterone. In pregnancy, decidual changes in the endometrium take place under the influence of progesterone. Progesterone is very important for the maintenance of pregnancy (*Progestin*= favours pregnancy).
2. *Cervix* The watery cervical secretions are changed to a viscid scanty secretion by progesterone.

3. *Vagina* Vaginal epithelium changes to that seen in pregnancy.
4. *Mammary gland* Along with oestrogen, progesterone is responsible for the development of the secretory apparatus in the breast and prepares the gland for lactation.
5. *Body temperature* Increase in the body temperature by 1°C during luteal phase beginning at ovulation is due to progesterone.

Adverse effects Headache, breast engorgement, rise in body temperature, edema, acne and mood swings may be seen. Progesterone is teratogenic.

Uses

1. *Contraception* (see below).
2. *Hormone replacement therapy (HRT)* Progestins are combined with oestrogens in HRT of postmenopausal women (given cyclically), oestrogen administration increases the risk of endometrial cancer—but supplementing it with a progestin counters this risk.
3. *Ovarian suppression* Progestins are used to suppress ovulation in dysmenorrhoea, endometriosis, dysfunctional uterine bleeding (DUB) and premenstrual syndrome.
4. *Threatened or habitual abortion* Efficacy in such patients is not proved.

5. *Endometrial carcinoma* Progestins are used as a palliative measure in cases with metastasis.

ANTIPROGESTINS

Mifepristone binds to the progesterone receptor and blocks the actions of progesterone. When given in early pregnancy—abortion occurs.

Mechanism of action Mifepristone blocks the progesterone receptors in the uterus which causes decidual breakdown; blastocyst gets detached, HCG and progesterone secretions fall. This in turn increases prostaglandin levels and stimulate uterine contractions. It also softens the cervix and facilitates expulsion of the blastocyst.

Uses

1. *Termination of pregnancy* Early pregnancy up to 9 weeks can be terminated with a single oral dose—600 mg of mifepristone followed 48 hr later by a prostaglandin to increase uterine contractions and facilitate expulsion of the blastocyst. **Adverse effects** include heavy bleeding, nausea and abdominal pain.
2. *Postcoital contraceptive* Mifepristone prevents implantation when given within 72 hrs after coitus. Regular use of mifepristone once a month as a contraceptive has been tried.

Table 51.1: Antagonists of sex hormones and their uses

Hormone	Receptor antagonist	Uses of antagonist
Oestrogen	Tamoxifen Clomiphene citrate	Breast cancer • Infertility • <i>In vitro</i> fertilization
Progesterone	Mifepristone	Termination of pregnancy
Androgen	Flutamide Cyproterone	Carcinoma prostate • Carcinoma prostate • Hypersexuality in men • Female hirsutism

HORMONAL CONTRACEPTIVES

Millions of women around the world use hormonal contraceptives making them one of the most widely prescribed drugs. When properly used, they are the most effective spacing methods of contraception. Hormonal contraceptives have greatly contributed to the control of population throughout the world.

Oral pills	Depot preparations
• Combined-pill • Mini-pill	• Injectables • Subcutaneous implants
• Postcoital pill	• Transdermal patches • Vaginal rings

Oral Pill

1. *Combined pill* contains low doses of an oestrogen and a progestin. They are highly efficacious (success rate 98%). Ethinyloestradiol or mestranol (in the dose of 30-50 mcg) are the oestrogens used. Newer progestins like desogestrel and norgestimate cause least side effects. The pill is started on the 5th day of the menstrual cycle, taken daily for 21 days followed by a gap of 7 days during which bleeding occurs. This is monophasic regimen.

Oral contraceptives are also available as biphasic or triphasic preparations (Table 51.2). This reduces the amount of hormones needed and more closely mimics menstrual cycle.

If a woman misses a pill, she should take 2 pills the next day and continue the course. If more than 2 pills are missed, then that course should be withdrawn, should follow an alternative method of contraception for that particular cycle and restart the course on the 5th day of the next menstrual cycle. If the woman has conceived, the pregnancy should be terminated because these hormones are

teratogenic. However, recent studies have found low doses of the hormones to be non teratogenic.

2. *Mini-pill* A low dose progestin is taken daily without a gap. Oestrogen and its accompanied long-term adverse effects are also eliminated. But efficacy is lower, menstrual cycles may be irregular and is therefore not popular.

3. *Postcoital contraceptives* Postcoital pills act by preventing implantation. The earlier they are given the better. High dose of an oestrogen was used earlier. Combination of oestrogen and progestins is now preferred due to lower doses needed and lesser side effects reported. The pill should be started within 72 hours of coitus and has an efficacy of 90-98%.

Benefits of combined pills

1. Effective and convenient method of contraception.
2. Reduced risk of ovarian cancers (ovarian stimulation by gonadotropins)
3. Reduced risk of endometrial cancers (progesterone antagonises the endometrial proliferation induced by oestrogens)
4. Reduced incidence of pelvic inflammatory disease and ectopic pregnancy.
5. Menstrual benefits—less menstrual blood loss, less iron-deficiency; premenstrual tension and dysmenorrhoea are less intense.

They are advocated as an emergency method in situations following rape or contraceptive failure.

Depot preparations are given as:

1. *Progestin injections*
 - a. Intramuscular injections at 3-6 months intervals, e.g. depot medroxyprogesterone acetate (DMPA 150-400 mg) or Norethisterone enanthate (NET EN 200 mg).

Table 51.2: Oral contraceptive preparations

Regimen	Oestrogen	Progestin	Trade name
Monophasic	E E 50 mcg E E 30 mcg	Norgestrel 0.5 mcg Levonorgestrel 0.15 mcg	OVRAL-G OVRAL-L
Biphasic	E E 35 mcg	Norethindrone 0.5 mcg (10 days) 1 mcg (11 days)	—
Triphasic	6 days E E 30 mcg next 5 days E E 40 mcg next 10 days E E 30 mcg	Levonorgestrel 50 mcg Levonorgestrel 75 mcg Levonorgestrel 125 mcg	TRIQUILAR
Mini-pill	Nil	Norgestrel 75 mcg	OVRETTE
Postcoital pill	Diethyl stilboestrol (25 mg/day for 5 days) Or Combined pill (2 stat and 2 after 12 hr) Or Levonorgestrel (0.75mg –1 pill stat and 1 after 12 hr)	—	— OVRAL ECEE-2

EE-Ethinyl estradiol

b. Implants—They are implanted under the skin. *Norplant* capsules implanted subcutaneously in the forearm or upper arm work for 5 years.

Disadvantages (i) Amenorrhoea is frequent
(ii) Permanent sterility may occur.

2. Combined injectable contraceptives—oestrogen and progestin injected at monthly intervals are highly effective.
3. Transdermal patch—containing a progestin and an oestrogen is applied once a week for 3 weeks and the next week withdrawal bleeding occurs. It is well accepted as it is more convenient.
4. Vaginal rings—containing low dose of levonorgestrel is placed in the vagina for 3 weeks of the cycle and then removed for one week. The hormone is absorbed gradually through the vaginal mucosa.

Mechanism of action of oral contraceptives

Combined pills act by multiple mechanisms.

1. They prevent ovulation - By a negative feedback on the hypothalamus, progesterone decreases GnRH pulses and thereby LH release which is essential for ovulation.
2. Oestrogens suppress FSH release by negative feedback on the pituitary. As a result the ovarian follicle fails to develop.
3. Progesterone also inhibits oestrogen-induced mid-cycle LH surge.
4. Progesterone renders the cervical mucous thick and unfavourable for sperm penetration.
5. OCs alter the uterine endometrium making it not favourable for implantation.
6. OCs also adversely influence the coordinated contractions of the cervix, uterus and fallopian tubes which are required for transport of ovum, sperm as well as fertilisation and implantation.

Adverse Effects

- Headache, migraine headache in some women, nausea, vomiting, oedema, breast tenderness, amenorrhoea and irregular menstrual cycles may be commonly seen.
- Weight gain, acne, mood swings and hirsutism may occur.

More severe side effects include -

- Cardiovascular effects - in women above 35 years, OCs may increase the risk of MI and venous thromboembolism. OCs may also increase the coagulability of blood. But the newer low-dose preparations are found to be safer when used in healthy women with no other risk factors for MI or thromboembolism.
- Hypertension-The high dose preparations may precipitate hypertension in some women. But the newer low dose preparations are safer.
- Cancers OCs may increase the incidence of cervical, breast and other cancers—but the risk is not significant.
- Cholestatic jaundice and gallstones Incidence may be higher in high dose preparations.
- Glucose tolerance OCs may impair glucose tolerance—but the newer low dose preparations do not carry such risk.

Contraindications to combined pill:

- Thromboembolic and cerebrovascular disease
- breast cancers
- liver disease
- OCs should be used with caution in diabetes, hypertension, convulsive disorders, oedema and CCF.

Centchroman is a nonsteroidal oral contraceptive developed by CDRI, Lucknow. It has antioestrogenic and antiprogestogenic activity and may act by preventing implantation. Onset of action is quick (< 60 minutes) and duration of action is 7 days. Dosage (SAHELI, CENTRON) 30 mg twice a week for 3 months followed by once a week till contraception is desired (The tablet should be continued without withdrawing for menstruation). Success rate claimed is 97-99% and is devoid of the side effects of hormonal contraceptives. It is well tolerated.

Drugs Acting on the Uterus

Uterine Stimulants (Ecbolics)

Drugs which stimulate the uterine contractions are oxytocin, ergometrine and prostaglandins. They are used in obstetrics. Oxytocin is used for induction of labour; ergometrine is used to prevent and control postpartum bleeding. Prostaglandins—PGE₂ and PGF_{2α} are used to induce mid trimester abortion and for cervical priming.

Uterine Relaxants (Tocolytics)

Tocolytics are drugs that reduce uterine motility. Beta adrenergic agonists like salbutamol, terbutaline and isoxuprine and other drugs like ethyl alcohol, calcium channel blockers, aspirin and magnesium sulphate have tocolytic properties. They are used to delay premature labour, in threatened abortion to inhibit uterine contractions and in dysmenorrhoea.

Androgens and Anabolic Steroids

Androgens are produced chiefly in the testes and small amounts in the adrenal cortex. In the females, small amounts of androgens are produced in the ovary and adrenal cortex. Testosterone is the most important natural androgen. In the adult male, 8-10 mg of testosterone is produced daily. Secretion is regulated by gonadotrophins and GnRH.

Physiological actions In the male, testosterone is essential for the development of secondary sexual characters and sex organs. It is necessary for normal spermatogenesis and is important for maintaining sexual function in men. Testosterone promotes bone growth, enhances the muscle mass, protein synthesis and positive nitrogen balance—has anabolic actions.

Mechanism of action is similar to other steroids. Androgens bind to androgen receptors on the target cells, the complex moves to the nucleus where it stimulates protein synthesis.

Adverse effects Masculinization and acne in females, hepatotoxicity, increased libido and precocious puberty can occur in young boys. With large doses, salt and water retention, suppression of spermatogenesis resulting in infertility can be seen. Feminizing effects like gynaecomastia in men can occur as some androgens are converted to oestrogens.

Uses

1. *Testicular failure* Androgen replacement therapy in primary and secondary testicular failure.
2. *Other uses* Androgens may be used in senile osteoporosis and carcinoma of the breast in premenopausal women.

ANABOLIC STEROIDS

Anabolic steroids are synthetic androgens with higher anabolic and low androgenic activity. These are believed to enhance protein synthesis and increase muscle mass. But with higher doses, the relative anabolic activity is lost. Methandienone, nandrolone, oxandrolone and stanozolol are some anabolic steroids available at present. *Adverse effects* are similar to those caused by androgens.

Uses

1. *Catabolic states* Anabolic steroids may benefit patients following surgery, trauma, prolonged illness and debilitating conditions. Given during convalescence, the negative nitrogen balance is corrected, appetite improves and there is a feeling of well being.
2. *Senile osteoporosis* seen in elderly males respond by formation of new bone tissue.

3. *Growth stimulation in children* Anabolic steroids promote linear growth in prepubertal boys. They may be used only for short periods—but actual benefit on final height is not established.

4. *Other uses* Anabolic steroids are tried in chronic renal failure to reduce nitrogen load on the kidneys. They may benefit in refractory anaemias with bone marrow failure.

Abuse in athletes Anabolic steroids enjoy a reputation for improving athletic performance. When combined with adequate exercise, the muscle mass increases. But the dose used by athletes is very high and is associated with serious adverse effects like testicular atrophy, sterility and gynaecomastia in men and virilizing effects in women; increased aggressiveness, psychotic symptoms and increased risk of coronary heart disease in both sexes. Moreover, there is no evidence that athletic performance improves. Hence the use of anabolic steroids by athletes has been banned and is medically not recommended.

ANTIANDROGENS

Cyproterone acetate—a derivative of progesterone competitively binds to androgen receptors and thus blocks the actions of androgens. It also has progestational activity. Cyproterone is used to treat severe hypersexuality in males, in carcinoma prostate and in female hirsutism. *Flutamide* is a potent competitive antagonist at androgen receptors. It is used with GnRH/leuprolide in the treatment of carcinoma prostate.

Danazol—has weak androgenic, anabolic and progestational activity. It suppresses gonadotrophin secretion from the pituitary.

It is used in endometriosis in women and precautious puberty in boys.

Finasteride inhibits the enzyme 5- α reductase and thus inhibits the conversion of testosterone to its active metabolite dihydrotestosterone which acts mainly in the male urogenital tract. Finasteride is used in benign prostatic hypertrophy to reduce the prostate size.

DRUGS USED IN MALE SEXUAL IMPOTENCE

Sexual impotence is the inability of a man to have satisfactory sexual intercourse due to inability to have and maintain an erection. Very often it is psychological while in some cases there could be an organic cause. Several drugs have been tried including testosterone, yohimbine, papaverine and antidepressants. The recent introduction—Sildenafil (Viagra) has been a success in a large percentage of them.

Sildenafil (Viagra)

Sildenafil is the first agent to be effective orally for the treatment of erectile dysfunction. Sildenafil inhibits the enzyme phosphodiesterase in the penis and thus prolongs the life of cyclic GMP. This causes relaxation of smooth muscle in the corpus cavernosum and vasodilation—both resulting in cavernosal engorgement and penile erection.

Sildenafil is given orally (50-100 mg) 1 hour before sexual activity.

Adverse effects and precautions Due to vasodilation—headache, dizziness and nasal stuffiness can occur. It potentiates the hypotensive action of nitrates and is contraindicated in patients on nitrates and in patients with coronary artery disease. Elderly men above 60 years need less dose (25 mg).

Insulin and Oral Hypoglycaemics

Diabetes mellitus is a chronic metabolic disorder characterised by hyperglycaemia and altered metabolism of carbohydrates, lipids and proteins. It is a common condition affecting 1-2% of population with a strong hereditary tendency.

Diabetes mellitus can be of 2 types.

Type I Insulin dependent diabetes mellitus (IDDM) is an autoimmune disorder where antibodies destroy the β cells of the islets of Langerhans. It usually occurs in the young children and adolescents (hence called juvenile onset diabetes mellitus).

Type II Non-insulin dependent diabetes mellitus (NIDDM) is of maturity onset. Most patients are obese. There is both reduced sensitivity of tissues to insulin and impaired regulation of insulin secretion.

Prolonged hyperglycaemia results in various complications including premature atherosclerosis, retinopathy, nephropathy and gangrene of the limbs. This is thought to be due to reduced blood supply to these structures - because of thickening of the capillary walls. Hence, it is necessary to maintain normal blood glucose levels though diabetes mellitus as such does not cause significant troublesome symptoms. Treatment helps to prevent or delay the onset of complications of diabetes.

INSULIN

In 1921 Banting and Best first obtained insulin in the form of pancreatic extract. In

1922 the extract containing insulin was first used on a 14 years old boy suffering from severe diabetes mellitus with excellent response. Insulin was then purified in a few years.

Chemistry, synthesis and secretion Natural insulin is a polypeptide synthesized from the precursor proinsulin. It has two peptide chains - A chain (21 amino acids) and B chain (30 amino acids) linked by disulphide bridges. Human insulin differs from bovine insulin by 3 amino acids and from porcine insulin by 1 amino acid. Hence porcine insulin is closer to human insulin.

Insulin is stored in granules in the β islet cells of the pancreas. Normal pancreas releases about 20-40 units of insulin everyday. The secretion is regulated by factors like food, hormones and autonomic nervous system. Blood glucose concentration is the main factor. The islets of Langerhans are composed of 4 types of cells— β cells secrete insulin, α (A) cells glucagon, δ (D) cells somatostatin and P cells secrete pancreatic polypeptide.

Insulin is metabolised in the liver, kidney and muscle.

Actions of Insulin

1. *Carbohydrate metabolism* Insulin stimulates the uptake and metabolism of glucose in the peripheral tissues especially skeletal muscles and adipose tissue. It inhibits glucose

production in the liver by inhibiting gluconeogenesis and glycogenolysis.

By the above actions, insulin lowers the blood glucose concentration.

2. *Lipid metabolism* Insulin inhibits lipolysis in adipose tissue and promotes the synthesis of triglycerides. In diabetes, large amounts of fat are broken down. The free fatty acids so formed are converted by the liver to acetyl CoA and then ketone bodies. This results in ketonaemia and ketonuria.

Insulin indirectly enhances lipoprotein lipase activity resulting in increased clearance of VLDL and chylomicrons. In insulin deficiency, there is hypertriglyceridaemia.

3. *Protein metabolism* Insulin facilitates amino acid uptake and protein synthesis and inhibits protein break down—anabolic effect.

In diabetes, there is increased catabolic effect and negative nitrogen balance.

Mechanism of action Insulin acts by binding to specific receptors.(Fig 53.1). Insulin receptor is made up of two α and two β subunits. Insulin receptors are present on almost all cells in the body. Insulin binds to these receptors present on the surface of target

cells. This binding stimulates tyrosine kinase activity in the β subunit. This in turn activates a cascade of phosphorylation and dephosphorylation reactions which stimulate or inhibit the enzymes involved in the metabolic actions of insulin.

Side Effects

1. *Hypoglycaemia* is the most common complication of insulin therapy. It may be due to too large a dose, inappropriate time of administration, unusually small meal or vigorous exercise. Symptoms include sweating, palpitation, tremors, blurred vision, weakness, hunger, confusion, difficulty in concentration and drowsiness. Severe hypoglycaemia may result in convulsions and coma.

Treatment Oral glucose or fruit juice like orange juice or in severe cases IV glucose promptly reverse the symptoms.

2. *Allergy* This is due to the contaminating proteins. Urticaria, angioedema and rarely anaphylaxis can occur. It is rare with purified preparations and human insulin.

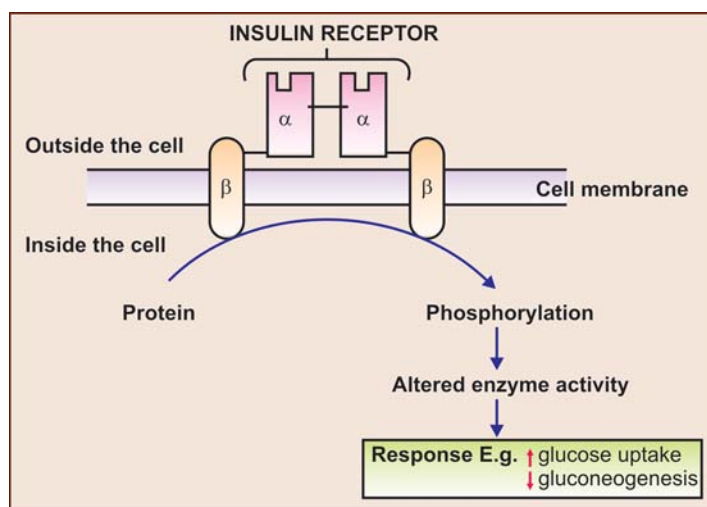


Fig. 53.1: Mechanism of action of insulin

3. *Lipodystrophy* Atrophy of the subcutaneous fat at the site of injection may be due to immune response to contaminating proteins.

Lipohypertrophy *i.e.* enlargement of subcutaneous tissue can also occur due to the local action of insulin. Insulin absorption may be irregular from such areas. This can be prevented by frequently changing the sites of injection. Lipodystrophy is rare with purified preparations.

4. *Oedema* Some severe diabetics develop oedema which is self-limiting.

Preparations of Insulin (Table 53.1)

Insulin preparations differ in their source and duration of action. Based on the source they may be grouped as Bovine, Porcine and Human insulins. Conventional preparations are obtained from bovine and porcine pancreas. They may be short, intermediate or long-acting (Table 53.2). All preparations are given SC. Only regular (plane) insulin can be given IV in emergencies. Insulins are destroyed when given orally. Doses are expressed as units of insulin and should be calculated in each patient by monitoring blood glucose and *glycosylated haemoglobin* levels. Mixtures of short and acting and intermediate/long-acting preparations are given for a rapid onset and long duration of action.

Disadvantages of the conventional preparations are that:

- i. They are allergenic because of the impurities (1%) and their animal source.
- ii. They are not very stable.

Hence highly purified preparations and human insulins are now made available. *Highly purified insulins* are mostly porcine insulins purified by more developed purification techniques including gel filtration and ion exchange chromatography. The

Table 53.1: Preparations of insulin

<i>Conventional Insulins</i>	
Short and Rapid acting	Regular Semilente
Intermediate acting	Lente Isophane insulin (NPH)
Long acting	Ultralente Protamine zinc insulin
<i>Highly Purified Insulins</i>	
Single peak insulin	Regular Lente
Monocomponent insulins	Regular Lente
<i>Human Insulin</i>	
	Regular Lente Isophane
<i>Insulin Analogs</i>	
	Insulin lispro Insulin aspart Insulin glargine
<i>Insulin Mixtures</i>	
	Combinations of 20-50% regular with 80-50% NPH Insulins

contaminating protein content is negligible. They are available in short and long acting forms.

Human insulins are produced by recombinant DNA technology. Human insulin is available as regular, NPH, lente and ultralente preparations - but they are all expensive. They are absorbed more rapidly; dose needed is lesser (10%).

Highly purified insulins and human insulin have the following advantages over conventional insulins-

1. they are less antigenic
2. more stable
3. lesser chances of resistance
4. lesser chances of lipodystrophy.

Indications for highly purified/human insulins:

1. Allergy to conventional preparations
2. Insulin resistance

Table 53.2: Onset and duration of action of insulin preparations

Preparation	Onset (hrs)	Duration (hrs)
<i>Short-acting</i>		
Regular (plane, soluble)	0.5-1	8
Semilente (Insulin zinc suspension/amorphous)	1	14
<i>Intermediate-acting</i>		
Lente (Insulin zinc suspension)	2	24
NPH (Neutral protamine hagedorn or Isophane insulin)	2	24
<i>Long-acting</i>		
Ultra lente (Insulin zinc suspension/crystalline)	6	36
PZI (Protamine zinc insulin)	6	36

3. Lipodystrophy at the site of injection

4. Pregnancy

Insulin analogs with favourable pharmacokinetic properties have been synthesized by genetic engineering. They are absorbed 3 times faster than human insulins—can be given (subcutaneously) 10 minutes before food; have lesser chances of hypoglycaemia. Blood glucose control is better than with regular insulin. Currently available analogs include insulin lispro, aspart and glargine. Insulin lispro and aspart are rapid and short acting while glargine is the long acting analog.

Insulin delivery devices like portable pen injectors and insulin pumps have been designed which make insulin administration more convenient.

Drug Interactions

1. β adrenergic blockers mask tachycardia, the important warning symptom of hypoglycaemia. They also prolong hypoglycaemia by inhibiting compensatory mechanisms acting through β_2 receptors.
2. Salicylates precipitate hypoglycaemia by enhancing both insulin secretion and β cell sensitivity to glucose.

Use of Insulin in Diabetes Mellitus

Insulin is effective in all types of diabetes mellitus. The dose should be adjusted as per the needs of each patient—guided by blood sugar levels.

Insulin resistance is said to be present when the insulin requirement is increased to > 200 U/day. It is due to the antibodies to insulin which partly neutralise it. This is rare with purified preparations and human insulin. Antibodies may also develop to contaminants and other added constituents like protamine. Hence in presence of resistance, it is necessary to change over to highly purified/human insulin. In some patients immunosuppression with corticosteroids like prednisolone may help.

ORAL HYPOGLYCAEMIC DRUGS

The main disadvantage of insulin is the need for injection. The advent of oral hypoglycaemics came as a boon to millions of NIDDM patients with early and mild diabetes. Sulfonylureas were the first oral antidiabetics (OAD) to be made available in 1950s. We now have 5 groups of oral hypoglycaemics and may be classified as follows—

CLASSIFICATION

1. Sulfonylureas
 - I generation*
 - Tolbutamide,
 - chlorpropamide
 - acetohexamide, tolazamide
 - II generation*
 - Glibenclamide, glipizide,
 - gliclazide, glimepiride
2. Biguanides
 - Phenformin, metformin
3. Meglitinides
 - Repaglinide, nateglinide
4. Thiazolidinediones
 - Troglitazone, rosiglitazone,
 - pioglitazone
5. Alpha glucosidase inhibitors
 - Acarbose, miglitol

Sulfonylureas

A sulfonamide derivative used for its antibacterial effects in typhoid patients produced hypoglycaemia. This observation led to the development of sulfonylureas.

Mechanism of action Sulfonylureas reduce the blood glucose level by:

1. stimulating the release of insulin from the pancreatic β cells.
2. increasing the sensitivity of peripheral tissues to insulin.
3. increasing the number of insulin receptors.
4. suppressing hepatic gluconeogenesis.

Sulfonylureas bind to receptors on pancreatic β cells, and block the ATP - sensitive K^+ channels. This reduced K^+ conductance causes depolarization and Ca^{++} influx leading to increased insulin secretion. Thus some functional β cells are essential for the action of sulfonyl ureas.

First Generation Agents

Tolbutamide is short acting and is therefore associated with lesser risk of hypoglycaemia - hence it is safer in the elderly diabetics.

Chlorpropamide is long acting ($t_{1/2}$ 32 hrs) and can cause prolonged hypoglycaemia particularly in the elderly. *Tolazamide* has a slow onset of action. Use of first generation agents can result in several drug interactions.

Second Generation Agents

Second generation agents are more potent, have fewer side effects and drug interactions. But they can cause hypoglycaemia because of which they should be used cautiously particularly in the elderly. They are all contraindicated in renal and hepatic impairment.

Glibenclamide (*Gliburide*) is a commonly used sulfonylurea. It is longer acting – can be given once a day. It can cause hypoglycaemia and rarely flushing after alcohol consumption. *Glipizide* has a short $t_{1/2}$; food delays its absorption, it is less likely to cause hypoglycaemia.

Glimepiride is longer acting and can be given as a single morning dose.

Pharmacokinetics Sulfonylureas are well-absorbed orally, extensively bound to plasma proteins, metabolised in the liver and some are excreted in the urine. Hence they should be avoided in patients with renal or liver dysfunction. Dose - Table 53.3.

Adverse effects Second generation agents have fewer adverse effects. Hypoglycaemia is the most common adverse effect, least with tolbutamide due to its short $t_{1/2}$ and low potency.

Nausea, vomiting, jaundice, and allergic reactions can occur (Table 53.4). Patients on sulfonylureas may have an increase in the rate of cardiovascular death. However this is still controversial and sulfonylureas continue to be used.

Drug Interactions

I. Drugs that augment hypoglycaemic effect.

- NSAIDs, warfarin, sulfonamides – displace sulfonylureas from protein binding sites.

- Alcohol, chloramphenicol, cimetidine—inhibit metabolism

II. *Drugs that decrease the action of sulfonylureas*

- Diuretics and corticosteroids – ↑blood glucose levels.

Biguanides

Biguanides lower blood glucose level by insulin-like effects on the tissues. Mechanism of action is not clear. They

- Suppress hepatic gluconeogenesis.
- Inhibit glucose absorption from the intestines.
- Stimulate peripheral uptake of glucose in tissues in the presence of insulin.

Phenformin is not used therapeutically as it causes lactic acidosis. Metformin is safer with lower incidence of lactic acidosis. It does not cause hypoglycaemia since it is an euglycaemic agent.

Adverse effects Nausea, diarrhoea, and metallic taste are self-limiting. Rarely lactic acidosis can occur. Anorexia is advantageous as it helps in reducing body weight. Long-term use may interfere with vitamin B₁₂ absorption.

Meglitinides

Repaglinide and nateglinide are insulin secretagogues. Like sulphonylureas, meglitinides enhance the release of insulin by blocking the ATP dependent K⁺ channels in the pancreatic β cells.

Both repaglinide and nateglinide are rapidly absorbed from the gut; repaglinide has a $t_{1/2}$ of 1 hour. Both drugs can cause hypersensitivity reactions and hypoglycaemia – but the incidence is relatively lower with nateglinide. Gastrointestinal disturbances are common with repaglinide.

Meglitinides can be used in type 2 diabetes mellitus either alone or with biguanides.

Biguanides

- Have insulin-like effects
- Do not cause hypoglycaemia
- Weight reduction—due to anorexia
- Nausea, diarrhoea, metallic taste are transient
- Preferred in obese diabetics either alone or with sulfonylureas
- Contraindicated in renal, hepatic and cardiac diseases

Thiazolidinediones (TZDs)

Thiazolidinediones or glitazones are agonists at the PPAR γ receptors (gamma subtype of peroxisome – proliferator activated receptors.) TZDs activate the PPAR γ receptors and induce the synthesis of genes which enhance insulin action.

- TZDs increase insulin-mediated glucose transport into muscle and adipose tissue.
- reduce hepatic gluconeogenesis
- once a day administration
- low potential for hypoglycaemia
- ↑ HDL cholesterol
- no clinically significant drug interactions known so far.

Disadvantages

- 6-12 weeks of treatment is required to establish maximum therapeutic effect.
- May cause weight gain and anaemia.
- May cause oedema and precipitate or worsen CCF.
- Liver function should be monitored regularly.
- Troglitazone causes severe hepatotoxicity and therefore is not used now.

Uses—TZDs are used as adjuvants to sulphonylureas or biguanides in Type II diabetes mellitus. Though they can also be used as monotherapy in mild cases of type II diabetes, further studies are needed to prove their long term benefits.

α - Glucosidase Inhibitors

Acarbose an oligosaccharide and *miglitol* competitively inhibit the enzymes α - glucosidases present in the intestinal brush border and thereby prevent the absorption of carbohydrates. Monosaccharides like glucose and fructose are absorbed from the intestines while disaccharides and oligosaccharides are broken down into monosaccharides before being absorbed. This 'breaking down' is done by the enzymes α - glucosidases (e.g. sucrase, maltase, glycoamylase) and α - amylase present in the intestinal wall. α glucosidase inhibitors inhibit the hydrolysis of disaccharides and decrease carbohydrate absorption.

- Alpha glucosidase inhibitors reduce the glucose absorption from upper intestines thereby reducing post-prandial blood glucose levels.
- Alpha glucosidase inhibitors do not cause hypoglycaemia. But when used with other antidiabetics if hypoglycaemia occurs, glucose should be given and not sucrose because sucrase is inhibited.
- They may cause gastrointestinal disturbances including abdominal distention, flatulence and diarrhoea because of undigested carbohydrates

reaching the colon and then getting fermented.

α glucosidase inhibitors can be used alone in patients with predominantly postprandial hyperglycaemia or in combination with other oral antidiabetics or insulin.

TREATMENT OF DIABETES MELLITUS

The aim of treatment is to keep the blood sugar within normal limits and prevent complications of diabetes. For patients with IDDM, insulin is the only treatment.

Mild NIDDM may be controlled by diet, exercise and weight reduction. When not controlled, an oral hypoglycaemic should be given. Most NIDDM patients may require insulin sometime later in life.

Status of Oral Antidiabetics

Uncomplicated NIDDM patients not controlled by diet and exercise are given oral hypoglycaemics. Mild NIDDM patients with recent onset diabetes, age above 40 years at the onset of diabetes, obese with fasting blood sugar < 200 mg/dl are candidates for oral hypoglycaemics. They are convenient to use. Sulfonylureas are preferred, but when not adequately controlled, metformin can be added. Metformin has the advantages of

Table 53.3: Dose and duration of action of oral hypoglycaemics

Drug	Dose	Duration of action
Tolbutamide (RASTINON)	500 mg q 8-12 h	6-8 hr
Chlorpropamide (DIABINESE)	250-500 mg OD	36-48 hr
Glibenclamide (DAONIL, EUGLUCON)	5 mg q 12-24 h	18-24 hr
Glipizide	5-15 mg OD-BD	12-18 hr
Gliclazide	40-240 mg OD	12-24 hr
Glimepiride	1-4 mg OD	12-24 hr
Metformin (GLYCIPHAGE)	500 mg OD-BD	6-8 hr
Repaglinide	0.5-4 mg BD-TID	4-5 hr
Nateglinide	60-120 mg BD-TID	3-4 hr
Pioglitazone	15-45 mg OD	12-24 hr
Rosiglitazone	2-8 OD	24 hr
Acarbose	25-100 mg before each meal	—
Miglitol	25-100 mg before each meal	—

Table 53.4: Mechanism of action and prominent adverse effects of oral antidiabetics

Oral antidiabetics	Major mechanism	Adverse effects
Sulfonylureas (e.g. Tolbutamide, glibenclamide)	↑ insulin release from pancreas ↑ tissue sensitivity to insulin	Hypoglycaemia, cholestatic jaundice
Biguanides (<i>Metformin</i>)	↓ hepatic gluconeogenesis ↑ tissue sensitivity to insulin	Diarrhoea, metallic taste, rarely lactic acidosis
Meglitinides (Repaglinide, nateglinide)	↑ insulin release from pancreas	Hypoglycaemia
Thiazolidinediones (Rosiglitazone, pioglitazone)	PPAR γ agonist ↑ glucose transport into tissues ↓ hepatic gluconeogenesis	Weight gain, oedema, may ppt CCF, Risk of hepatotoxicity
α glucosidase inhibitors (Acarbose, Miglitol)	↓ glucose absorption ↓ hydrolysis of disaccharides	Flatulence, diarrhoea, abdominal distension

reducing appetite and being euglycaemic. In conditions like stress, surgery or complications of diabetes, insulin should be used. TZDs, meglitinides or α - glucosidase inhibitors may be used as monotherapy in mild NIDDM patients or as adjuvants along with sulfonylureas or biguanides. If diabetes is not controlled, patient should be switched over to insulin. In some patients, insulin may be supplemented with sulfonylureas as the latter increase the tissue sensitivity to insulin. For treatment of diabetic ketoacidosis (see page 402)–

Diabetes Mellitus and Dentistry.

Patients with diabetes need to maintain very good oral hygiene as they are prone for odontogenic, periodontal and other infections including a higher incidence of caries.

In well controlled diabetics, dental procedures generally do not require any special precaution. However, antibiotic coverage may be required.

In uncontrolled diabetics, infections and wound healing may be a problem even after minor procedures. If major dental procedures or surgery is to be undertaken, prior control of diabetes by the physician is needed. If the

patient is on only OAD, he may have to be switched over to insulin by the physician. Adequate antibiotic coverage is a must.

Dental procedures may often reduce food intake and diabetics may go into hypoglycaemia. Patient should be warned about it and insulin/OAD dose adjustment may rarely be required.

GLUCAGON

Glucagon is synthesized in the alpha (A) cells of the pancreatic islets of Langerhans; like insulin, the secretion of glucagon is regulated by nutrients—chiefly glucose, paracrine hormones and autonomic nervous system. Fasting stimulates glucagon secretion. It is degraded in the liver, kidney and plasma.

Actions Glucagon increases blood glucose level by glycogenolysis and gluconeogenesis in the liver. It evokes insulin release. It mobilises stored fat and carbohydrates. Glucagon increases the heart rate and force of contraction. It also relaxes the intestinal smooth muscles. Glucagon can be used in the emergency treatment of severe hypoglycaemia due to insulin. It can also be used in radiology of the bowel—as glucagon relaxes intestines.

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Agents Affecting Bone Mineral Turnover

Calcium and phosphorus are the most important minerals of the bone with 1-2 kg of calcium and 1 kg of phosphorus stored in it. Calcium and phosphorus metabolism are chiefly regulated by vitamin D and parathormone. Other hormones that also influence calcium and phosphorus metabolism are calcitonin, growth hormone, insulin, thyroid hormone, prolactin, glucocorticoids and sex hormones.

CALCIUM

Calcium is essential for tissue excitability, muscular excitation-contraction coupling,

secretion from glands, myocardial contractility and formation of bones and teeth. It also maintains the integrity of mucous membranes and cell membrane. Calcium is essential for normal blood coagulation.

Calcium is absorbed from the small intestines by a carrier mediated active transport. Normally about 30% of the dietary calcium is absorbed, while in Ca^{++} deficiency, the absorption increases under the control of vitamin D (Fig. 54.1). The normal plasma calcium level is 9-11 mg/dl. It is excreted in faeces, urine and sweat.

Adverse effects Oral calcium can produce constipation.

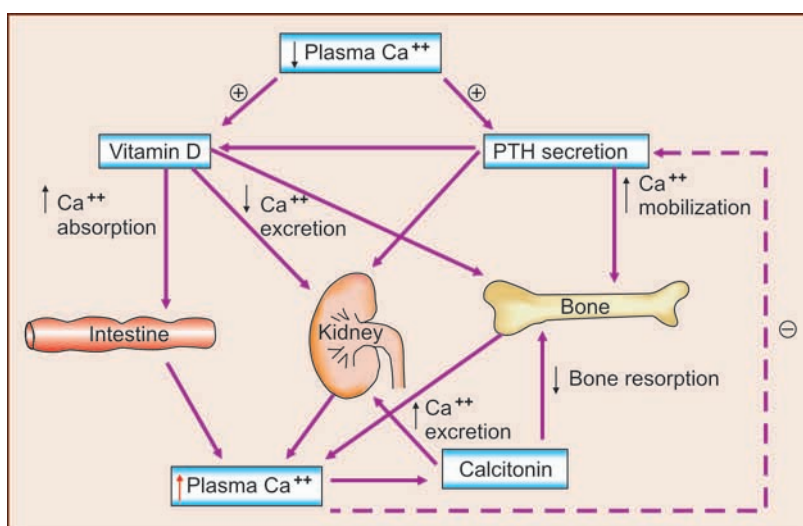


Fig. 54.1: Regulation of plasma calcium level

Uses

1. To prevent and treat calcium deficiency. Calcium supplements are given orally in children, pregnant and lactating women and in postmenopausal osteoporosis to prevent calcium deficiency.
Tetany: 5-10 ml IV calcium gluconate followed by 50-100 ml slow IV infusion promptly reverses the muscular spasm. The injection produces a sense of warmth. This is followed by oral calcium 1.5 g daily for several weeks.
2. Vitamin D deficiency rickets—calcium is given along with vitamin D.
3. As an antacid—calcium carbonate is used orally.
4. For placebo effect—IV calcium is used in weakness, pruritus and some dermatoses. The feeling of warmth produced by the injection could afford psychological benefit.

PHOSPHATE

Phosphates play a vital role in various enzymatic reactions, are important for the structure and function of the cells and are important constituents of teeth and bones. Phosphorus is absorbed by the small intestine and excreted through kidneys under the influence of parathormone.

Hypophosphataemia results in muscle weakness and abnormal bone mineralization.

PARATHYROID HORMONE (Parathormone, PTH)

Parathormone is a peptide secreted by the parathyroid gland. Secretion of PTH is regulated by plasma Ca^{++} concentration—low plasma Ca^{++} stimulates PTH release, while high levels inhibit secretion. Parathormone maintains plasma calcium concentration by mobilising calcium from the bone, promoting reabsorption of Ca^{++} from the kidneys and by stimulating the synthesis of calcitriol

which in turn enhances calcium absorption from the intestines. PTH also promotes phosphate excretion.

Hypoparathyroidism is characterised by low plasma calcium levels with its associated manifestations. Hyperparathyroidism which is most commonly due to parathyroid tumour produces hypercalcaemia and deformities of the bone.

PTH is not therapeutically used. It is used for the diagnosis of pseudohypoparathyroidism.

VITAMIN D

Vitamin D a fat-soluble vitamin, is a prehormone produced in the skin from 7-dehydrocholesterol under the influence of ultraviolet rays. It is converted to active metabolites in the body which regulate plasma calcium levels and various functions of the cells.

Hormones that influence bone metabolism

- Vitamin D
- Oestrogens
- Parathormone
- Glucocorticoids

Source

- Diet - as ergocalciferol (vitamin D_2) from plants.
- Fish, liver, fish liver oils - (cod, shark liver oil); milk.
- Cholecalciferol (vitamin D_3) is synthesized in the skin from 7-dehydrocholesterol.

Cholecalciferol (vitamin D_3) is converted to 25-OHD_3 (calcifediol) in the liver (Fig. 54.2) which is in turn converted to $1,25\text{-dihydroxy-cholecalciferol}$ (calcitriol) in the kidneys. Calcitriol is the active form of vitamin D while calcifediol is the main metabolite in circulation. Conversion of calcifediol to calcitriol is influenced by PTH and plasma phosphate concentration.

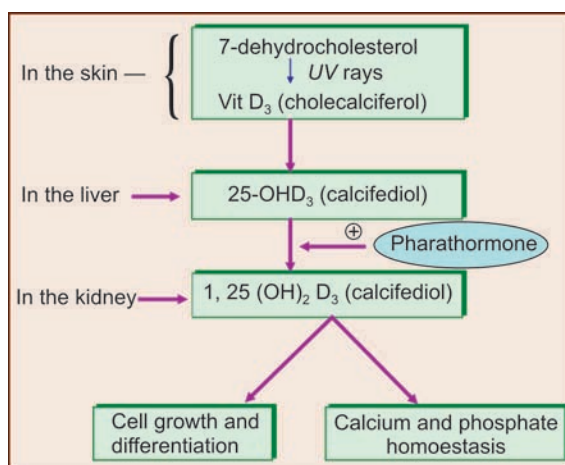


Fig. 54.2: Synthesis and functions of vitamin D

Actions The chief actions of calcitriol are:

- it stimulates calcium and phosphate absorption in the intestine
- mobilises calcium from bone by promoting osteoclastic activity
- increases reabsorption of Ca^{++} from kidney tubules.

Calcitriol is essential for normal bone mineralization. It is essential for skeletal muscles as well as cellular growth and differentiation.

Vitamin D deficiency results in low plasma calcium and phosphate levels with abnormal mineralization of the bone; causes rickets in children and osteomalacia in adults.

Daily requirement—400 IU (10 mg).

Pharmacokinetics Given orally, vitamin D is well-absorbed from the small intestines in the presence of bile salts. It is converted to 25-OHD₃ in the liver and circulates in the plasma, bound to a protein and is stored in the adipose tissue. Vitamin D is also degraded in the liver and the metabolites are excreted in the bile.

Preparations

- Calciferol capsules 25000; 50,000 IU.

- Cholecalciferol granules—oral 60,000 IU in Ig; 3,00,000 IU/ml; 6,00,000 IU/ml inj.
- Shark liver oil with vit D—1000 IU/ml, vit A—6000 IU/ml.
- Calcifediol (25(OH)D₃), alfa calcidiol (1- α (OH)D₃) and calcitriol (1,25(OH)₂D₃) are synthetic Vitamin D analogs available for use.

Adverse reactions High doses of vitamin D used for long periods result in hypervitaminosis D manifesting as generalised decalcification of the bones, hypercalcaemia, hyperphosphataemia resulting in weakness, drowsiness, nausea, abdominal pain, thirst, renal stones and hypertension. Hypervitaminosis D in children is most often due to unnecessary vitamin D supplementation by parents.

Uses

1. **Prophylaxis**—400 IU daily or 3,00,000 IU every 3-6 months IM prevents vitamin D deficiency. Adequate dietary calcium and phosphate intake is necessary. In the breastfed infants, from the first month onwards oral vitamin D supplements are needed. In obstructive jaundice, prophylactic 6,00,000 units vit D given IM prevents deficiency.
2. **Nutritional rickets and osteomalacia** 6,00,000 units IM repeated after 4-6 weeks is needed in rickets and osteomalacia along with calcium supplements.
3. **Vitamin D resistant rickets** is a hereditary disorder with abnormality in renal phosphate reabsorption. Phosphate with vitamin D is found to be useful.
4. **Vitamin D dependent rickets** is due to calcitriol deficiency (inability to convert calcifediol to calcitriol) and is treated with calcitriol.
5. **Senile osteoporosis** Oral vitamin D supplements with calcium may be tried.
6. **Hypoparathyroidism** Calcitriol with Ca^{++} supplements are beneficial.

CALCITONIN

Calcitonin is a peptide hormone secreted by the parafollicular 'C' cells of the thyroid gland. Secretion is regulated by plasma Ca^{++} concentration—high plasma Ca^{++} stimulates calcitonin release.

Actions The chief effects of calcitonin are to lower serum calcium and phosphate by its actions on the bone and kidney. It inhibits osteoclastic bone resorption and in the kidney, it reduces both calcium and phosphate reabsorption.

In general the effects are opposite to that of PTH. Calcitonin is used to control hypercalcaemia, Paget's disease, metastatic bone cancer and osteoporosis and to increase bone mineral density.

Other hormones that regulate bone turnover are glucocorticoids and oestrogens. Glucocorticoids antagonise vitamin D stimulated intestinal calcium absorption and enhance renal Ca^{++} excretion. Oestrogens reduce bone resorption by PTH and also enhance calcitriol levels. Oestrogen receptors are found in bone which suggests that they may also have a direct effect on bone remodeling.

DRUGS USED IN THE DISORDERS OF BONE

Drugs used in disorders of bone are:

- Bisphosphonates -
 Alendronate etidronate
 Pamidronate residronate
- Raloxifene (selective oestrogen receptor modulator)
- Vitamin D

Bisphosphonates are analogs of pyrophosphate; they inhibit bone resorption. Bisphosphonates get incorporated into bone matrix, are imbibed by osteoclasts and then incapacitate the osteoclasts resulting in reduced bone resorption. They also slow the formation and dissolution of hydroxyapatite crystals.

Fever, oesophagitis, gastritis and hypocalcaemia can occur. Long-term use can lead

to osteomalacia due to inhibition of bone mineralisation.

Uses Bisphosphonates are used in Paget's disease of the bone, hypercalcaemia and is tried in postmenopausal osteoporosis.

1. Paget's disease - Bisphosphonates relieve pain and induce remission.
2. Hypercalcaemia - Some malignancies are associated with hypercalcaemia. Intravenous pamidronate is useful in reducing plasma Ca^{++} levels.
3. Osteoporosis - Alendronate and residronate are tried with calcium and vitamin D for the prevention of postmenopausal osteoporosis.

Raloxifene is a SERM useful in women for the prevention of postmenopausal osteoporosis.

Agents used in the prevention and treatment of osteoporosis

Drugs may be used either to prevent bone resorption or promote bone formation or a combination of both in the prevention and treatment of osteoporosis. These agents reduce the risk of fractures in patients with osteoporosis.

I. Drugs that Prevent Bone Resorption

- Calcium ($\uparrow$ BMD*)
- Vitamin D ($\uparrow$ absorption of calcium)
- Oestrogen (prevents osteoporosis)
- Raloxifene – a SERM ($\uparrow$ BMD)
- Calcitonin (prevents bone resorption, $\uparrow$ BMD)
- Bisphosphonates - $\downarrow$ bone resorption, ($\uparrow$ BMD)
BMD – Bone mineral density.

II. Drugs that Promote Bone Formation

- Fluoride (in small doses $\uparrow$ osteoblastic activity - $\uparrow$ bone mass - but generally not preferred).
- Testosterone (in hypogonadal men)
- Anabolic steroids (in postmenopausal women).
- PTH analogs (are being tried).

Section 13

Miscellaneous Drugs

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Miscellaneous Drugs

IMMUNOPHARMACOLOGY

Immunosuppressants

Immunosuppressants are drugs which inhibit immunity. They may suppress cell mediated or humoral immunity or both. They are:

CLASSIFICATION

1. *T-cell inhibitors*
Cyclosporine, tacrolimus sirolimus, mycophenolate mofetil
2. *Cytotoxic drugs*
Azathioprine, methotrexate, cyclophosphamide, chlorambucil
3. *Glucocorticoids*
4. *Antibody reagents*
Muromanab CD3, Antithymocyte globulin

T-Cell inhibitors

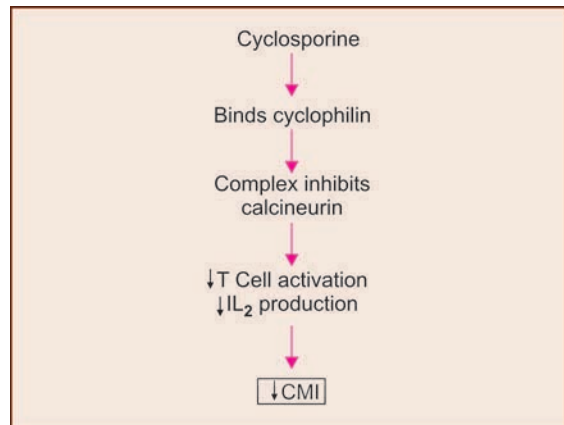
Cyclosporine is a cyclic peptide produced by a fungus *Beauveria nivea*.

Actions Cyclosporine acts at an early stage, selectively inhibits T cell-proliferation and suppresses cell mediated immunity. It can be given orally and intravenously.

Mechanism of Action

Cyclosporine binds to cyclophilin (an immunophilin) and this complex binds to and

inhibits the enzyme calcineurin phosphatase. This results in inhibition of T cell activation and IL-2 production. T cells do not respond to specific antigenic stimulation. Cyclosporine also suppresses the proliferation of cytotoxic T cells. Tacrolimus binds to another immunophilin and then the complex inhibits calcineurin.



Pharmacokinetics Cyclosporine is metabolised by microsomal enzymes in the liver. It can therefore interact with many drugs given concurrently.

Adverse effects include nephrotoxicity, hepatotoxicity, anorexia, gum hypertrophy and increased susceptibility to infections, hypertension, hyperglycaemia, hyperlipidaemia and hirsutism.

Uses

- *In organ transplantation* Cyclosporine is very effective for the prophylaxis and treatment of graft rejection in organ transplantation surgeries—like kidney, liver, bone marrow and other transplants.
- *Autoimmune disorders* Cyclosporine is also useful in some autoimmune disorders like rheumatoid arthritis as an alternative in patients who do not respond to methotrexate. Cyclosporin is also tried in severe psoriasis, atopic dermatitis, inflammatory bowel disease and nephrotic syndrome.

Tacrolimus is a macrolide antibiotic obtained from *Streptomyces tsukubaensis*. Its mechanism of action is similar to cyclosporine. Tacrolimus can be given both orally and parenterally but absorption from the gut is incomplete. It is extensively bound to plasma proteins.

Adverse effects include nephrotoxicity, gastrointestinal disturbances, hypertension, hyperglycaemia, tremors and seizures.

Sirolimus obtained from *Streptomyces hygroscopicus* acts by inhibiting calcineurin like cyclosporine. Sirolimus may be used in combination with other drugs for the prophylaxis of organ transplant rejection and in psoriasis and uveoretinitis.

Toxicity includes hyperlipidaemia, gastrointestinal disturbances and an increased risk of infections and lymphomas.

Mycophenolate mofetil a prodrug, is converted to mycophenolic acid, which inhibits guanine nucleotide synthesis and inhibits the proliferation and functions of lymphocytes.

Mycophenolate mofetil is indicated as an adjunct to other immunosuppressive drugs in the prophylaxis of transplant rejection.

CYTOTOXIC DRUGS

Cytotoxic drugs like azathioprine, cyclophosphamide and methotrexate inhibit cell mediated immunity (while cyclophosphamide predominantly suppresses humoral immunity). They are used in the prevention of graft rejection and in autoimmune disorders.

Glucocorticoids

Glucocorticoids have potent immuno-suppressant activity and are used in the prevention of organ transplant rejection and in autoimmune disorders.

Antibody Reagents

Muromonab CD3 is a monoclonal antibody to CD3 antigens on T lymphocytes. On intravenous administration, T cells disappear from the circulation within minutes. It is used with other immunosuppressants in organ transplantation. Fever, chills and pulmonary oedema may occur.

Antithymocyte globulin (ATG) binds to T lymphocytes and depletes them thereby suppressing immune response. It is used in the management of organ transplantation.

Infliximab is a monoclonal antibody and *etanercept* is a protein that blocks TNF α . They are useful in rheumatoid arthritis and Crohn's disease.

IMMUNOSTIMULANTS

Immunostimulating and immunomodulating agents are drugs that modulate the immune response and can be used to increase the immune responsiveness of patients with immunodeficiency as in AIDS, chronic illness and cancers. This is yet a developing field of pharmacology. The drugs currently used for this purpose are BCG and levamisole. BCG has been tried in cancers. Levamisole used in helminthiasis is also found to enhance cell-mediated immunity in humans. It has been tried in some cancers.

Interferons are cytokines with antiviral and immunomodulatory properties. Recombinant interferons α , β and γ are available for clinical use. They bind to specific receptors and bring about immune activation and increase host defences. There is an increase in the number and activity of cytotoxic and helper T cells and killer cells (See Page 308)

Interferons α , and β are mainly used for antiviral effects while interferon γ for its immunomodulating actions.

Interferons are indicated in several tumours including malignant melanoma, hairy cell leukaemia lymphomas, kasposi's sarcoma, condylomata acuminata and in viral infections.

ANTISEPTICS AND DISINFECTANTS

Disinfection is destruction of all pathogenic organisms but not spores. If spores are also killed, it is called *sterilization*. A *disinfectant* is used on *inanimate objects*.

Antiseptic is an agent that destroys micro-organisms and can be used on *living tissues*. The term *germicide* can be used for either drugs. Germicides are widely used in domestic products like soaps, tooth pastes and after-shave lotions.

Mechanism of action

Germicides may act by the following mechanisms—

1. Oxidation of bacterial protoplasm
2. Denaturation of bacterial proteins
3. Detergent like action
4. Competition with essential substrates for the important enzymes in the bacterial cell.

An ideal germicide should have a wide antibacterial spectrum, should be chemically stable, should have rapid action, non-irritating to the tissues, not interfere with wound healing activity even in presence of pus, exudates and tissue degradation products; it should not be absorbed into systemic circulation.

CLASSIFICATION

- | | |
|------------------------------|---|
| 1. <i>Acids</i> | Boric acid, Benzoic acid. |
| 2. <i>Alcohols</i> | Ethanol, Isopropyl alcohol |
| 3. <i>Aldehydes</i> | Formaldehyde, Glutaraldehyde. |
| 4. <i>Surfactants</i> | Soaps, Benzalkonium, Cetrimide, Cetylpyridinium chloride, Dequalinium chloride. |
| 5. <i>Phenol derivatives</i> | Phenol, Cresol, Resorcinol, Chlorhexidine, Chloroxylenol, Hexachlorophene. |
| 6. <i>Halogens</i> | Iodine, Iodophores, Chlorine, Chloramines. |
| 7. <i>Oxidizing agents</i> | Hydrogen peroxide, Potassium permanganate, Benzoyl peroxide. |
| 8. <i>Dyes</i> | Gentian violet, Methylene blue, Brilliant green, Acriflavin, Proflavine. |
| 9. <i>Metallic salts</i> | Mercurial compounds, Silver nitrate, Zinc compounds. |

Factors that influence the activity of germicidal agents

1. *Concentration of the drug and duration of contact* In general, higher the concentration of the antiseptic, greater is its effect. But alcohol is an exception to this and at 70% concentration maximum antiseptic effect is seen.
2. *Susceptibility of the organism* Spores and viruses are resistant to many antiseptics.
3. *Temperature* A rise in temperature will increase antiseptic activity.

Acids

Boric acid and sodium borate (borax) have weak bacteriostatic and fungistatic activity. Aqueous solutions of boric acid are used for irrigating eyes, bladder, vagina and large wounds.

Benzoic acid is an antibacterial (below pH 5) and antifungal agent used as a preservative in laboratory.

Salicylic acid has bacteriostatic, fungicidal and keratolytic properties. It is used as a dusting powder or 2% ointment for seborrhoeic dermatitis, warts and corns.

Alcohols

Ethyl alcohol is employed as an antiseptic at 60-90% concentration. The antiseptic activity decreases above 90%. It rapidly denatures the bacterial proteins (page 143).

Disadvantages

1. It has poor activity against spores, some viruses and fungi
2. Irritant—causes burning when applied on open wounds
3. Alcohols are flammable—should be allowed to evaporate before using cautery or laser surgery.

Uses Ethyl alcohol is used to clean the skin before injections and surgeries.

Isopropyl alcohol is more potent and more toxic than ethanol. It is used in 68-72% concentration as skin antiseptic.

Aldehydes

Formaldehyde is a gas at room temperature used for fumigation; the 40% aqueous solution is noncorrosive and has a broad antimicrobial spectrum. It has a pungent odour and is an irritant—highly irritating to respiratory mucous membranes and eyes. Formaldehyde is also a carcinogen and OSHA has set standards to limit exposure of health care workers to formaldehyde.

Mechanism of action Aldehydes act by alkylation of chemical groups in proteins and nucleic acids.

Uses Formaldehyde gas is used for fumigation and for sterilizing instruments which cannot be moistened with solution. Formaldehyde 40% solution (100% formalin) in water is used

for disinfection of surgical instruments and gloves; embalming and preservation of tissues. Fibre optic endoscopies, respiratory therapy equipment, haemodialysers and dental hand pieces which cannot withstand high temperatures of steam sterilisation are disinfected with formaldehyde.

Automatic circulating baths are used which increase penetration of aldehyde solution into the instruments and decrease operator exposure to the chemical. It's rapidity of action increases by making a solution in 70% propanol.

Glutaraldehyde is a dialdehyde used as a 2% solution. It is bactericidal, sporicidal, fungicidal and viricidal. pH should be between 7.4 and 8.5. It is less irritant than formaldehyde; has greater sporicidal activity; does not damage lenses and cementing material in endoscopes. Glutaraldehyde is superior to formaldehyde for sterilising rubber, plastic and metal appliances. Two per cent solution is used for local application in idiopathic hyperhidrosis of palms and soles.

Surfactants

Surfactants are chemicals that lower the surface tension of solutions and are termed detergents. They may be anionic, cationic, ampholytic surfactants or polysorbates.

Anionic surfactants e.g. soaps.

- They dissociate in aqueous solutions to form a large and complex anion which lowers the surface tension.
- Effective for gram-positive and acid fast organisms.
- Microorganisms are enmeshed in the lather and washed away on rinsing.
- Anionic surfactants have a narrow spectrum; precipitate in hard water; cause drying of the skin.

Preparations

1. Potassium hydroxide or sodium hydroxide + vegetable oil.
2. Sodium lauryl sulphate—is effective in hard water.

Cationic surfactants-e.g. Benzalkonium chloride, Cetrimide, Cetylpyridinium chloride, Dequalinium chloride. Cationic surfactants dissociate into large cations.

They are:

- active against gram-positive and gram-negative organisms (less active against spores, viruses and fungi)
- most effective in neutral solution
- non-irritating and safe
- incompatible with anionic surfactants
- absorbed by cotton and rubber
- one of the most commonly used germicidal agents.

Benzalkonium chloride (ZEPHIRAN) has an aromatic odour and is soluble in water.

- 1: 1000 solution for cleansing skin
- 1:2000 for mucous membranes and denuded skin
- 1:20,000 for irrigation of the bladder and urethra
- It is also used for (1: 1000-4000) storing sterilised surgical instruments. But instruments should be thoroughly washed before use.

Cetrimide (CETAVLON) 1% solution is used like above. It is also used as a cream. It is very effective for cleaning wounds. In combination with chlorhexidine it is the most popular antiseptic. SAVLON is cetrimide 3% + chlorhexidine.

Dequalinium chloride is used in gum paints and lozenges.

Cetylpyridinium chloride is used in mouthwashes and lozenges.

Phenol Derivatives

Phenol is one of the oldest antiseptics introduced by Lord Lister in 1867. It is bactericidal and fungicidal but has poor action against spores and viruses. It acts by denaturing the bacterial proteins. It also has a mild local anaesthetic action. Phenol rapidly penetrates even intact skin and mucous membrane. It is a protoplasmic poison.

Phenol is extremely irritant to exposed tissues (corrosive)-when swallowed, it burns buccal, oesophageal and gastric mucous membrane.

Uses Phenol is used to disinfect urine, faeces, sputum of patients and is sometimes used as antipruritic because of its local anaesthetic action.

Cresol is methylphenol, which is as toxic as phenol but is more active. It is used as a disinfectant for utensils and excreta.

Lysol is cresol with soap solution. It has higher antiseptic activity and is a useful disinfectant for hospital and domestic use.

Chloroxylenol (DETTOL) is a less toxic chlorinated phenol, effective against gram-positive and gram-negative organisms. Surgical dettol contains 1.4% of chloroxylenol for skin; 6.25% for instruments and 1 to 3% in antiseptic cream.

Hexachlorophene This chlorinated phenol acts by inhibiting bacterial enzymes and causing lysis. It is effective mainly against gram-positive organisms and has weak action against gram-negative organisms. It is odourless and non-irritating to use on skin. It is used in soaps for surgical scrubbing, for cleaning the skin in obstetrics, carbuncles and seborrhoeic dermatitis. It may cause allergic reactions. It also reduces body odour by preventing bacterial decomposition of organic material and therefore is used as a deodorant. In USA, hexachlorophene was used to wash newborn babies which resulted in brain damage in such babies and therefore use of > 3% hexachlorophene is banned.

Chlorhexidine (HIBITANE) is effective against gram-positive, gram-negative organisms and fungi. It is rapid acting and non-irritating. SAVLON is chlorhexidine + cetrimide.

Halogens

Iodine is one of the oldest antiseptics. It has a broad spectrum of activity, is a powerful bactericidal, sporicidal, fungicidal and

viricidal agent. The activity is inhibited by organic material but enhanced by alcohol.

Disadvantages It is irritating, painful, stains the area, and may delay wound healing. Rashes, fever and generalised skin eruptions may develop in some patients who are sensitive to iodine. Prolonged systemic use causes iodism.

Uses of iodine

1. *Tincture iodine* (I_2 in KI + alcohol)-used to clean skin before surgery. Iodine crystals are used to sterilize water for soaking vegetables and cleaning before use.
2. *Mandl's paint* (Compound Iodide paint) is used in the treatment of tonsillitis and pharyngitis.
3. *Iodine ointment*-as fungicide in ringworm. Iodides have no antibacterial action.

Iodophors Iodophors are soluble complexes of iodine with surfactants like detergents. The detergents serve as carriers and slowly release iodine, e.g. Povidone iodine (BETADINE)-5% solution; Piodine-10% solution. **Advantages** Iodophors are non-irritating, non-staining, water-soluble, less toxic and non-sensitizing to the skin.

Uses Used for preoperative scrubbing, skin preparation, disinfection of instruments, as local antiseptic in boils, furunculosis, burns, ulcers, ringworm and in oral/vaginal moniliasis.

Chlorine is a potent germicide and is bactericidal against several gram-positive and gram-negative organisms in a very low concentration (0.1 PPM in 30 seconds). It also destroys protozoa and viruses. The antibacterial activity of chlorine is reduced in presence of organic matter since they bind chlorine and therefore need higher concentration of free chlorine. Chloramines are compounds that release chlorine slowly.

1. *Chlorinated lime* (bleaching powder) is obtained by the action of chlorine on lime. It is used for disinfection of water in swimming pools and water for drinking.

2. *Chloramine* is an organic chloride. The freshly prepared solution is used for mouthwash, for irrigating the bladder and urethra.

3. *Eusol* is a solution of chlorinated lime with boric acid.

Oxidizing Agents

Hydrogen peroxide is a colourless and odourless liquid. It liberates nascent oxygen when applied to tissues and then oxidizes bacteria and necrotic tissue. On application, there is effervescence and this helps in removing tissue debris, ear wax, etc. Hydrogen peroxide has poor penetrability and the action is of short duration. On keeping, it loses its potency. It is also a deodorant.

Uses Hydrogen peroxide is used for cleansing wounds, abscesses and for irrigation. In dentistry, it is used to clean septic sockets and root canals and also as a mouthwash and deodorant gargle. It is used as ear drops while removing ear wax.

Potassium permanganate is an oxidizing agent and an astringent. The purple crystals are water-soluble. It acts by liberating oxygen which oxidizes bacterial protoplasm. Organic matter reduces its activity and the solution gets decolourised. It promotes rusting; concentrated solution is caustic and causes burns and blistering.

Uses

- 1:4000-1:10000 solution of potassium permanganate is used for gargling, irrigating cavities, urethra and wounds.
- For stomach wash in alkaloidal poisoning (except atropine and cocaine because these are not efficiently oxidized).
- 1% solution in mycotic infections like athlete's foot.
- 5% solution as a styptic.
- Topically to oxidise venom in case of snake and scorpion bite.
- To purify well water.
- To disinfect vegetables and fruits.

Dyes

Gentian violet (aniline dye, crystal violet or medicinal gentian violet) is effective against gram-positive organisms and fungi. Staining is the only disadvantage. It is a non-irritant and potent antiseptic. 0.5-1% solution is used topically on furunculosis, burns, boils, chronic ulcers, infected eczema, thrush, ringworm and mycotic infections of the skin and mucous membranes.

Brilliant green Actions are similar to gentian violet. Used as a 0.5-1% solution in the treatment of burns, impetigo and infected wounds like gentian violet.

Methylene blue is used systemically in cyanide poisoning as it converts methaemoglobin to haemoglobin.

Acriflavine and proflavine are acridine dyes active against gram-positive bacteria and gonococci (proflavine is better). They are non-irritant; efficacy is unaffected by organic matter but is increased in alkaline medium; 1: 1000 solution is used in infected wounds and burns, 2% pessary in vaginitis and cervicitis.

Triple dye lotion contains gentian violet 0.25% + brilliant green 0.25% + acriflavine or proflavine 0.1 %-it is used in burns dressing.

Metals

Silver compounds have antiseptic, astringent and caustic properties. Silver nitrate kills microbes rapidly and the action is prolonged due to slow release of silver ions from silver proteinate that is formed by an interaction with tissue proteins. The reduced silver gets deposited and stains the tissues black.

Silver nitrate is used for the prophylaxis of ophthalmia neonatorum.

Silver sulfadiazine is active against *Pseudomonas* and is used in burn wounds.

Colloidal silver compounds slowly release silver. They are non-corrosive, non-irritant, non-astringent and have better penetrability used as nasal and eyedrops.

Zinc salts like zinc oxide has astringent and mild antiseptic properties. It is used as an ointment or lotion in eczema, impetigo and psoriasis.

Mercury compounds act by inhibiting sulphhydryl enzymes of bacteria. They are bacteriostatic and are poor antiseptics-not commonly used.

CHELATING AGENTS

Heavy metals bind to and inactivate the functional groups (ligands) of essential tissue enzymes. By this they interfere with normal cell functions which require these ligands. Heavy metals cannot be metabolised in the body.

Chelating agents or heavy metal antagonists bind the heavy metal ions and make them non-toxic. The chemical complex formed is called chelate (*Chele* = claw; in Greek). The process of complex formation is chelation. The complex so formed is water-soluble and is eliminated by the kidneys.

The clinically useful chelating agents are CaNa_2EDTA , dimercaprol, d-penicillamine and desferrioxamine. Chelating agents are more effective in preventing the utilization of ligands than in reactivating them—hence, the earlier they are given, the better.

Calcium disodium edetate (CaNa_2EDTA) chelates several divalent and trivalent metals like zinc, manganese, iron and lead. It is used in the treatment of lead poisoning. Given parenterally, lead deposits in the bone are mobilised, chelated and excreted through kidneys.

Adverse effects include nephrotoxicity, fatigue, fever, myalgia and dermatitis.

CaNa_2EDTA is mainly used in lead poisoning. It can also be used in zinc,

manganese and iron poisoning. Sodium edetate is used in severe hypercalcaemia.

Dimercaprol is a colourless, oily liquid developed by the British during World war II as an antidote to lewisite—an arsenical war gas. Hence it is also known as British Anti-lewisite or BAL. Dimercaprol chelates arsenic, mercury, lead and other heavy metals. It is given IM; appropriate plasma concentrations should be maintained.

Adverse effects are dose related and include hypertension, tachycardia, vomiting, sweating, burning sensation in the lips and mouth and headache.

Dimercaprol is used in arsenic and mercury poisoning; also used in lead poisoning with CaNa_2EDTA .

Unithiol

Unithiol is a water soluble analog of dimercaprol that can be given both orally and parenterally. It enhances the excretion of mercury, arsenic and lead. Adverse effects are mild and include allergic reactions. Unithiol may be used in mercury, lead and arsenic poisoning.

Succimer

Succimer is another water soluble analog of dimercaprol. It protects against acute arsenic poisoning and it is also effective in lead and mercury poisoning. It can be given both orally and intravenously. Succimer is used in the treatment of chronic lead poisoning and in mercury and arsenic poisoning. Anorexia, nausea, vomiting, diarrhoea and skin rashes can occur.

d-Penicillamine is prepared by degradation of penicillin but has no antibacterial activity. It chelates copper, mercury, zinc and lead. It is orally effective.

Toxicity Patients allergic to penicillin may develop anaphylaxis; dermatitis may occur

in some. On long-term use renal, haematological, dermatological and other toxicities can occur.

Uses

1. Treatment of copper, mercury and lead poisoning.
2. Wilson's disease (hepatolenticular degeneration)—copper is deposited in the liver and brain causing degeneration.
3. Rheumatoid arthritis (Page 186).
4. Cystinuria—promotes excretion of cysteine by forming soluble complexes and prevents formation of cysteine stones.

Desferrioxamine isolated from *Streptomyces pilosus*, chelates iron. It has a high affinity for iron, forms stable complexes and removes iron from haemosiderin and ferritin. It does not chelate the iron in haemoglobin and cytochromes. It is given parenterally (Page 223).

Toxicity Allergic reactions range from rashes to anaphylaxis (rare), diarrhoea, muscle cramps and blurred vision.

Uses

1. Acute iron poisoning—desferrioxamine is the drug of choice.
2. Chronic iron poisoning—as in thalassaemia patients who receive repeated blood transfusion.

Deferiprone chelates iron and is orally effective. It is used in thalassemia major to chelate iron as an alternative to desferrioxamine.

VITAMINS

Vitamins are organic compounds essential for normal metabolism in the body. They are supplied by the diet. A balanced diet supplies adequate amounts of vitamins to fulfill the daily requirement. The requirement is increased during periods of rapid growth,

pregnancy and lactation. Vitamin deficiencies result in characteristic signs and symptoms.

Vitamins are grouped into fat-soluble and water-soluble vitamins (Table 55.1).

FAT-SOLUBLE VITAMINS

Vitamin A

Vitamin A is present in the diet as retinol, dehydroretinol or as carotenoids. Carotenoids are pigments present in green yellow vegetables and fruits and is converted in the body to retinol.

Source Green leafy vegetables, carrots, mango, papaya, eggs, milk, butter, cheese, liver and fish liver oils. Maximum content is in Halibut liver oil - 9,00,000 mg/100 gm.

Physiological functions Vitamin A has an important role in dark adaptation. It is essential for the synthesis of rhodopsin, the photosensitive pigment of rods. Vitamin A is also essential for maintenance of the integrity of epithelial cells, for growth and cell-mediated immunity.

Signs and symptoms of deficiency Xerophthalmia (dryness of eyes), Bitot's spots in the conjunctiva, night blindness, diarrhoea, dry and rough skin are seen in early stages. In the later stages, keratomalacia, perforation of the cornea, necrosis and blindness can occur.

Daily requirement—3000-5000 IU/day.

Uses

In the prophylaxis and treatment of vitamin A deficiency.

1. Prophylaxis—3000-5000 IU/day in presence of increased requirement.
2. Treatment—50,000-1,00,000 IU intramuscularly or orally for 1-3 days followed by oral supplementation.
3. Acne—Retinoic acid or synthetic analogs of vitamin A like tretinoin or isotretinoin are used.

Hypervitaminosis A Since vitamin A is a fat-soluble vitamin, it accumulates in the body on prolonged administration. The symptoms are dry skin (hyperkeratosis), anorexia, fever, alopecia, anaemia, oedema, headache, skin ulcers and tenderness over the bones.

Vitamin D See Page 373 *Vitamin K* See Page 234

Vitamin E
Vitamin E or Alpha tocopherol is present in wheat germ oil, rice germ oil and soya bean oil.

Physiological role Vitamin E acts as an antioxidant. It prevents the damage due to free radicals in normal metabolic reactions. Vitamin E is essential for normal structure and function of the nervous system. It is also required to maintain the integrity of the biological membranes. Vitamin E deficiency in animals results in reproductive and haemopoietic system abnormalities, degenerative changes in the spinal cord and heart. Daily requirement is 10-15 mg.

Uses Clinically vitamin E deficiency in human beings is not known. It has been tried in G-6-PD deficiency, sterility, menopausal syndrome and other conditions with no definite evidence of obvious benefit.

WATER-SOLUBLE VITAMINS

Vitamin B-complex

B-complex group of vitamins includes thiamine, riboflavin, nicotinic acid, pyridoxine, pantothenic acid, biotin and cyanocobalamin.

Thiamine (Vitamin B₁, Aneurine)

Sources Pulses, outer layers of cereals, rice polishings, peas, nuts, green vegetables, egg and meat.

Physiological role Thiamine is converted to thiamine pyrophosphate which acts as a coenzyme in carbohydrate metabolism.

Daily requirement 1-2 mg.

Symptoms of deficiency Thiamine deficiency produces *Beriberi*.

Dry beriberi is characterised by peripheral neuritis and muscular atrophy.

Wet beriberi The characteristic features are dependent oedema and high output cardiac failure. Wernicke's encephalopathy and Korsakoff's psychosis are also thought to be due to thiamine deficiency.

Uses

1. Prophylactically in presence of increased demand as in pregnancy, lactation and infants.
2. Beriberi—50 mg daily parenterally. Once the patient recovers, maintenance dose of 10 mg/day is given orally.
3. Chronic alcoholics—50 mg daily.
4. Empirical use—thiamine is tried in several neurological and cardiovascular disorders and morning sickness.

Riboflavin (Vitamin B₂)

Sources Milk, egg, liver, meat, grains and green leafy vegetables.

Physiological function Flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) containing the active form of riboflavin are coenzymes in various oxidation-reduction reactions.

Symptoms of deficiency Angular stomatitis, glossitis, seborrhoeic keratosis of the nose, ulcers in the mouth, dry skin, burning sensation in the plantar surface of the feet, vascularization of the cornea and alopecia.

Uses Riboflavin is used for the prevention and treatment (2-10 mg) of riboflavin deficiency.

Nicotinic Acid and Nicotinamide (Vitamin B₃)

Nicotinic acid and nicotinamide are together known as *niacin*.

Sources Rice polishings, liver, fish, milk, eggs, nuts and pulses.

Physiological functions Nicotinic acid is converted to nicotinamide. Nicotinamide adenine dinucleotide (NAD) and its phosphate (NADP) are coenzymes involved in several oxidation-reduction reactions.

Nicotinic acid is also a lipid-lowering agent.

Symptoms of deficiency Niacin deficiency results in Pellagra characterised by dermatitis, diarrhoea and dementia. Other symptoms include: pigmentation of the skin, stomatitis, glossitis, headache, insomnia, hallucinations, confusion and megaloblastic anaemia. Chronic alcoholics, people living on maize as the staple diet, patients with malabsorption and cirrhosis develop pellagra.

Uses

1. Prophylaxis and treatment of pellagra (50-500 mg).
2. Nicotinic acid is used in hyperlipoproteinaemia (see Page 236).

Pyridoxine (Vitamin B₆)

Sources Cereals, legumes, liver, milk, meat and eggs.

Physiological functions Pyridoxal phosphate is a coenzyme involved in the synthesis of several amino acids, biogenic amines and other compounds like GABA.

Symptoms of deficiency Glossitis, peripheral neuritis, anaemia, dermatitis and low seizure threshold due to decreased GABA levels in the brain.

Uses

1. Prophylaxis and treatment of pyridoxine deficiency.
2. INH induced peripheral neuritis—pyridoxine is used both for prophylaxis and treatment.
3. Convulsions in infants due to pyridoxine deficiency.

Table 55.1: Sources, recommended daily allowances and deficiency symptoms of various vitamins in the diet (for adults)

<i>Vitamin</i>	<i>Important dietary sources</i>	<i>Daily allowance</i>	<i>Deficiency symptoms</i>
<i>Fat soluble vitamins</i>			
Vitamin A	Green leafy vegetables, carrots, mango, papaya, eggs, milk, butter, cheese, liver and fish liver oils	3000-4000 IU	Night blindness, xerophthalmia, hyperkeratosis of skin and epithelial tissues
Vitamin D	Liver, egg yolk, fish liver oils, milk, butter	200-400 IU	Rickets, osteomalacia
Vitamin E	Wheat germ, nuts, cereals, eggs, green leafy vegetables	10-15 mg	Not known
Vitamin K	Green leafy vegetables, liver, meat, cheese, egg yolk and tomatoes	50-100 mg	Hypoprothrombinaemia, haemorrhage
<i>Water soluble vitamins</i>			
Vitamin B complex			
Thiamine (B ₁)	Cereals, rice polishing, liver, egg yolk	1.2-1.4 mg	Beriberi, peripheral neuritis, anorexia
Riboflavin (B ₂)	Milk, cereals, pulses, leafy vegetables, eggs and meat	1.5-2 mg	Stomatitis, glossitis, cheilosis, vascularisation of cornea
Nicotinic acid (Niacin B ₃)	Rice polishings, cereals, pulses, groundnut, liver, meat, fish.	20 mg	Pellagra - diarrhoea, dermatitis, dementia; glossitis, stomatitis, delusions, confusion
Pantothenic acid	Rice polishings, whole grains, meat, egg yolk	4-7 mg	Weakness, fatigue, burning sensation in the feet
Pyridoxine (B ₆)	Whole grains, pulses, green vegetables, milk, liver, egg yolk	2 mg	Peripheral neuritis, glossitis, stomatitis
Biotin	Liver, nuts, egg yolk	0.1-0.2 mg	Not known
Folic acid	Leafy vegetables, milk, liver, meat, cereals	100-200 mg	Megaloblastic anaemia, glossitis, GI disturbances
Vitamin B ₁₂	Milk, egg yolk, liver, meat, fish	1-2 µg	Megaloblastic anaemia, demyelinating, neurological disorders of the spinal cord
Vitamin C	Goose berry (amla), citrus fruits, green vegetables and tomatoes, germinating pulses	50 mg	Scurvy - petechiae, bleeding gums, easy bruising, delayed wound healing, anaemia, weakness

4. 'Morning sickness' in pregnancy—pyridoxine may reduce vomiting by an unknown mechanism.

Pantothenic Acid

Sources Wheat, cereals, milk, peanuts, liver, egg yolk and vegetables.

Physiological role Pantothenic acid is converted to coenzyme A which is involved in several metabolic reactions. Pantothenic acid deficiency in human beings is not known. Experimentally induced deficiency results in fatigue and paraesthesia. Calcium pantothenate is a component of multivitamin preparations.

Biotin

Biotin is an organic acid found in liver, nuts, egg yolk and other foods. Biotin deficiency in humans is not known. Experimentally induced deficiency results in dermatitis, anorexia, alopecia and glossitis. Biotin is a coenzyme in several metabolic reactions. It is present in many multi-vitamin preparations. Avidin, a protein present in egg white prevents the absorption of biotin.

VITAMIN B₁₂, FOLIC ACID (see Page 225)

VITAMIN C (ASCORBIC ACID)

Sources Citrous fruits, tomatoes, goose berry, green vegetables and potatoes are rich in vitamin C.

Physiological role Ascorbic acid is involved in several metabolic reactions including oxidation reduction reactions and in cellular respiration. It is essential for the integrity of connective tissue, for the development of cartilage, bone and teeth and for wound healing.

Symptoms of deficiency Vitamin C deficiency results in scurvy characterised by connective tissue defects resulting in haemorrhages in

subcutaneous tissues, petechiae, ecchymoses, impaired wound healing, tender bleeding gums, deformed teeth, brittle bones, anaemia and growth retardation.

Uses

1. Prevention of vitamin C deficiency—50-100 mg daily.
2. Scurvy—500-1000 mg daily.
3. Common cold—large doses (0.5-1.5 gm) of vitamin C has been tried as prophylactic against common cold with controversial benefits.
4. To acidify urine.

GENE THERAPY

Gene therapy is the replacement of defective gene by the insertion of a normal, functional gene. It is the genetic modification of cells for the prevention or treatment of a disease. Gene transfer may be done to replace a missing or defective gene or provide extra-copies of a normally expressed gene. Gene therapy is aimed at genetically correcting the defect in the affected part of the body. Unlike all other drugs which only alter the rate of normal cell functions, gene therapy can confer new functions to the cell.

Vectors

Gene transfer requires the use of vectors to deliver the DNA material. An ideal vector should be safe and effective in inserting the therapeutic gene into the target cells. Physical, chemical and biological vectors have been tried.

- Physical vectors - DNA is complexed with substances like lipids and administered.
- Chemical vectors - Liposomes are used to carry genes into the cells.
- Biological vectors - The most important biological vectors are viral vectors. Viruses invade cells and use the metabolic

processes of these host cell for replication. This property of viruses helps to deliver the gene — adenoviruses and retroviruses are used for this purpose.

Therapeutic Applications of Gene Therapy

Gene therapy is at present a developing area. Though originally it was seen as a remedy for inherited single gene defects, gene therapy has now been found to be useful in several acquired disorders. The principal applications are in single gene defects like thalassaemia, cystic fibrosis and haemoglobinopathies and in the treatment of cancer, cardiovascular diseases, atherosclerosis, immunodeficiency disorders—particularly AIDS; anaemia, Alzheimer's disease and many infectious diseases. Some examples are-

1. *Growth hormone deficiency* - Growth hormone gene is transferred to myoblasts and these are implanted in patients.
2. *Familial hypercholesterolaemia* - LDL receptor gene is introduced into liver cells.
3. *Cancer*-
 - a. introducing the gene which makes the malignant cells sensitive to drugs.
 - b. inactivating the expression of oncogenes.
 - c. introducing genes that attaches to cancer cells and make them susceptible to host defense cells.
 - d. introducing genes to healthy cells to protect them from cytotoxic drugs.
4. *HIV infections*
 - a. Introducing genes coding for CD₄ cells that could inactivate HIV before entering the cell itself.
 - b. Introducing genes that enhance immunity against HIV.
5. *Diabetes mellitus* - Introducing insulin gene into the liver which can produce insulin.
6. *Coronary atherosclerosis* - Prevention of restenosis and ischaemia in coronary vessels by genes which inhibits the growth of vascular endothelial cells.

Section 14

Dental Pharmacology

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Dental Pharmacology

DENTIFRICES

Dentifrices are therapeutic aids meant for cleaning the teeth with the help of a toothbrush. They are available in the form of powders, liquids and paste, e.g. toothpastes and tooth powders. Though the prime purpose of a dentifrice is to assist the brush in cleaning the teeth, addition of certain substances like fluoride and antiseptics can afford additional benefits. The ingredients are:

1. Abrasive Agents

Dental abrasives are fine powdered substances which assist the scouring action of the toothbrush. They are inorganic salts of low solubility, e.g. prepared chalk, calcium phosphate, calcium and magnesium carbonates; magnesium oxide, ferric oxide, charcoal, silicates, powder pumice, kaolin and stannic oxide. The abrasive powder should be fine to avoid scratching of the teeth surfaces. Abrasives are also available as pastes. Generally powders are more powerful abrasives than pastes.

Uses

1. Polishing the teeth and fillings.
2. Cleaning the teeth.
3. In toothpastes and tooth powders.

2. Detergents

Detergents are cleansing agents which act by:

- (i) lowering surface tension, i.e. they possess emulsifying properties.
- (ii) dissolving fatty substances and mucus plaques.
- (iii) foaming—on scrubbing the teeth, detergents foam and act as lubricants.
- (iv) loosening the debris adhering to the teeth.
- (v) some of them also liberate oxygen and have antiseptic properties.

Thus detergents act as deodorants, e.g. sodium lauryl sulphate and soaps. Sodium lauryl sulphate—a pale yellow powder is effective in both acid and alkaline medium and in hard water. It is also used as a skin cleanser and in medicated shampoo.

3. Antiseptics

The small amount of antiseptics used in dentifrices may not be sufficient to afford adequate antiseptic action. Antiseptics used in dentistry are thymol, menthol, eugenol, benzoic acid, boric acid, myrrh, calcium and magnesium peroxide. Thymol is a powerful antiseptic and a deodorant used in mouthwashes and gargles. Eugenol has the odour of clove and is also a local anaesthetic commonly used for dental filling.

4. Sweetening Agents

Sweetening agents are substances used to impart a sweet taste to a pharmaceutical preparation. They are used to make the use of dentifrice more pleasant and acceptable. Saccharine sodium is commonly used in tooth powders and is intensely sweet. It is an artificial sugar 500 times sweeter than sugar and can be used as a dilute (1%) solution. Saccharine has no caloric value and is excreted unchanged within 24 hours. It is stable and nontoxic. Saccharine is less likely to encourage the development of caries when compared to other carbohydrates. It enhances the palatability. Though sucrose can also be used, it causes fermentation and is therefore not preferred.

5. Colouring Agents

Colouring agents are used to make the preparation more attractive for commercial purpose. Bright colours like cherry red, blue and green are used. Liquor rubri imparts red colour while methylene blue gives blue colour and chlorophyll is employed for green colour. Most colours used commercially are synthetically produced, though some of them may also be obtained from natural sources like plants, animals or minerals. Only premitted colour can be used in dentifrices.

6. Flavouring Agents

Flavouring agents are substances used to impart a pleasant smell and taste to the preparation so that it is more palatable. Though natural flavouring agents are available, synthetic flavours are preferred because of their easy availability. Generally fruity and spicy flavours are preferred. Peppermint, lemon, mint and pineapple are some natural flavours; synthetic flavours include alcohols, aldehydes, esters and fatty acids.

7. Other Agents

Other agents used in dentifrices include

- (i) binding agents like mucilage of tragacanth, gum acacia and bentonite; They help to bind the liquid and solid phases together in a paste.
- (ii) humectants like glycerine and sorbitol prevent drying up of the paste.
- (iii) Antacids like sodium bicarbonate neutralize acidity in the oral cavity.

A good dentifrice should be pleasant in taste, odour and consistency; should not damage the gums or the teeth.

OBTUNDENTS

Obtundents are agents that diminish dentine sensitivity. They are used to make the excavation painless. Obtundents act by one of the following mechanisms.

1. *Paralysing the sensory nerves*, e.g. phenol, menthol, thymol, clove oil, camphor, benzyl alcohol
2. *Precipitating proteins* Astringents like silver nitrate, zinc oxide and zinc chloride.
3. *Destruction of nervous tissue*, e.g. Absolute alcohol (Table 56.1).

But, the disadvantages with the use of obtundents are: pulp may shrink and irritants may stimulate the formation of secondary dentine. After the advent of local anaesthetics, the use of obtundents has declined.

ANTISEPTICS

Antiseptics used in dentistry are phenol, cresol, chloroxylenol, hexachlorophene, chlorhexidine, sodium hypochlorite, iodine and iodophors and oxidising agents like hydrogen peroxide, and sodium perborate; alcohol and benzalkonium chloride. For details see page 378.

MUMMIFYING AGENTS

Agents used to harden and dry the tissues of the pulp are called mummifying agents.

Table 56.1: Some obtundents, their mechanisms of action, advantages and disadvantages

<i>Obtundent</i>	<i>Mechanism of action</i>	<i>Advantages</i>	<i>Disadvantages</i>
Phenol	• Protoplasmic poison—paralyses nerves • Initial irritation followed by numbness	• Rapid action • Does not stain healthy dentine • Penetrability can be increased by combining with KOH and glycerine	• Infected dentine is darkened • Poor penetrability
Thymol Menthol Clove oil Camphor	• Paralyse sensory nerves—initial irritation followed by numbness	• Combination of these oils has rapid action	• Clove oil may stain the dentine yellow
Silver nitrate	• Astringent—precipitates superficial proteins	• Rapid action	• Stains the dentine black • Penetrability is poor
Zinc chloride	• Similar to silver nitrate	• Rapid action • Does not stain the teeth	• Initial pain is sharp
Paraformaldehyde	• Acts by release of formaldehyde which precipitates proteins	• Painless • Non-staining	• Slow action • Formaldehyde may penetrate pulp to cause inflammation

This hardening makes the tissues resistant to infection. Astringents and antiseptics are used in combination as a paste for this purpose. Some mummifying agents are:

1. *Liquid formaldehyde* It is used with zinc oxide and glycerine to harden the tissues.
2. *Paraform*—acts by slow release of formaldehyde and is used in combination with zinc oxide and glycerine.
3. *Iodoform*—acts by liberation of iodine. It is made into a paste with eugenol, phenol, tannic acid and glycerol for use in dental practice.
4. *Tannic acid*—is an astringent, precipitates proteins and hardens the tissues. The tissues may also shrink.

BLEACHING AGENTS

Bleaching agents are used to remove pigmentation of the teeth. Oxidising agents

like sodium peroxide and perhydrol, reducing agents like sodium thiosulphate and other agents like chlorides, hydrogen peroxide and ultraviolet rays have been used as bleaching agents. Hypochlorites remove silver and iron stains; sodium thiosulphate removes iodine stains while chlorinated lime is used to remove stains by aniline dyes.

STYPTICS

Styptics are local haemostatics. They are used to arrest local bleeding following tooth extraction and other dental procedures (Page 233)

MOUTHWASHES

Mouthwashes are solutions containing active ingredients meant for cleansing and deodorising the oral cavity. 15-30 ml of the diluted solution is used for gargling and

rinsing the mouth. Mouthwashes contain astringents, antiseptics and/or obtundents, flavouring and sweetening agents. Prolonged use of concentrated solutions result in staining.

Types of Mouthwashes

1. Antiseptic and astringent mouthwash—for soreness under dentures. They harden the mucous membrane.
2. Obtundent mouthwash—for sensitive oral lesions.
3. Detergent mouthwash—for cleansing and deodourising action.

Uses

1. Soreness under dentures.
2. Sensitive oral lesions.
3. Postoperative and other bedridden patients for deodourising the oral cavity and to maintain oral hygiene; mouthwashes are refreshing.
4. In halitosis.
5. Stomatitis.
6. Surgical impaction—after removal of impacted tooth.

Chlorhexidine (CHLORHEX REXIDINE) and Povidine iodine (BETADINE) are some commonly used mouthwashes.

ASTRINGENTS

Astringents are agents which precipitate superficial proteins when applied to the skin or mucous membrane. They form a protective coating and harden the surface. Astringents check minor haemorrhages—arrest capillary oozing as they promote clotting and precipitate proteins on the bleeding surface. Astringents are therefore used as obtundents, styptics and mummifying agents.

Types of Astringents

1. Vegetable astringents—tannic acid, gall.
 2. Metallic astringents—salts of zinc, copper, iron, aluminium and silver; also alum.
 3. Miscellaneous—alcohol, dilute acids.
- Uses* Astringents are used as mouthwashes, paints, lotions and dentifrices in aphthous ulcers, stomatitis, gingivitis and as local haemostatics.

DISCLOSING AGENTS

Dental plaques are relatively invisible. Certain agents (dyes) and iodine containing solutions may be used to make the supra-gingival plaques visible and such agents are called disclosing agents.

Dyes used as disclosing agents are as follows.

1. Erythrosin

Erythrosin tablets are dissolved into a solution or chewed to dissolve in the mouth. It stains the plaque area red but also may stain soft tissues. It is the most widely used disclosing agent.

2. Fluorescein Dye

On application, fluorescein dye stains the plaque yellow. It does not stain the soft tissues. But special light is required to see the stained plaque. It is more expensive.

3. Two-tone Dyes

A solution containing a combination of two dyes is used. Mature plaques are stained blue, while new plaques are stained red.

Advantages

- Dyes used as disclosing agents help to differentiate mature and immature plaques.
- They do not stain the gingival tissues.

4. Iodine Containing Solutions

Iodine containing solutions have been used as disclosing agents but have the disadvantage of causing a high incidence of allergic reactions. They also have an unacceptable taste. Hence iodine solutions are not preferred.

Methods of application To stain the plaque, solutions of disclosing agents may be used as follows:

- (i) Painting the teeth with a cotton swab
- (ii) Rinsing the mouth
- (iii) As tablets/wafers to be chewed dissolving it in the saliva. The mouth should then be rinsed with water.

SIALOGOGUES AND ANTISIALOGOGUES

Sialogogues are agents which enhance salivary secretions. Pilocarpine is generally used as a sialogogue though other drugs like bethanechol, and anticholinesterases like neostigmine also reduce salivary secretions. **Cevimeline** a newly introduced drug enhances salivary secretion by directly stimulating the muscarinic receptors. It is used to treat dry mouth in patients with Sjögren's syndrome.

- (i) Sialogogues are used to treat acute symptoms of sialoadenitis that may be seen in sialolithiasis. Surgical excision is required in most cases.
- (ii) Xerostomia-often follows radio-therapy of the head and neck. It may be troublesome because it causes difficulty in speaking and swallowing. It may be treated with pilocarpine.
- (iii) Sjögren's syndrome-cevimeline is used.

Antisialagogue

An antisialagogue is a substance that reduces salivary secretion. Propanthelene bromide an atropine substitute is commonly used for this purpose though atropine and many other anticholinergic drugs also decrease salivary secretion.

Uses

1. Sialoceles—An antisialagogue is used to suppress glandular function during healing or to encourage spontaneous resolution of the sialocoele. Propanthelene bromide (Pro-banthine) is given in the dose of 15 mg orally 4 times a day half an hour before food.
2. Post surgical—An antisialagogue is used for a short period following surgeries of the salivary glands and salivary ducts. Temporary reduction in the flow of saliva is thought to be helpful in faster wound healing.
3. In post-traumatic parotid fistulas and sialoceles.
4. Trauma to the salivary gland and salivary ducts.

ANTICARIES DRUGS

Caries is a degenerative condition characterised by decay of hard and soft parts of the teeth.

Fermentation of carbohydrates in the oral cavity results in the production of acids like lactic acid. These acids convert the insoluble calcium salts of the teeth into soluble salts (decalcification) which are easily removed. The oral flora produce proteolytic enzymes which digest the organic enamel matrix. Thus both organic and inorganic matter of the teeth are destroyed. As the process continues, the pulp is penetrated and the infection may gain access into the systemic circulation.

Fluorides Fluorine, a halogen, is the most electronegative of all elements and is therefore highly reactive. The efficacy of fluoride in the prophylaxis of dental caries has been well-established.

Mechanism of action Fluorides alter the physicochemical properties of the teeth as follows:

1. Fluorides inhibit bacterial enzymes which produce acids and therefore prevent decalcification of the teeth.

2. Fluorides convert the hydroxyapatite of enamel and dentine to fluorapatite which is more resistant to destruction by acids. Thus fluorides make the outer layers of enamel harder and more resistant to demineralization.
3. Fluorides also stimulate remineralization of the enamel.

Fluoridation of water supplies Fluoridation of drinking water is the most effective measure in preventing dental caries—if consumed prior to eruption of the permanent teeth. Several large-scale studies have established the beneficial effects of optimum fluoridation of communal water supplies in preventing caries. The optimum level of fluoride is 0.5-1 ppm and is found to be safe and effective. More than 1-2 ppm result in toxicity—cause dental fluorosis.

When communal water fluoridation is impracticable, table salt can be fluorinated. *Topical fluoride* Topical use of high doses of fluorides effectively prevents caries, It may be used as:

Fluoride dentifrices Several commercial preparations containing fluoride salts are available. Sodium fluoride, sodium monofluorophosphate or stannous fluoride are the salts used in such dentifrices. Mouth should be thoroughly rinsed and dentifrice should not be swallowed; children should be specially warned—to avoid fluorosis. Used twice a day regularly, they effectively prevent caries.

Fluoride mouthrinses 0.2% sodium fluoride solution containing 900 ppm of fluoride, retained in the mouth for one minute—to be used twice a week is effective in preventing caries.

Topical application by a dentist of 2% sodium fluoride or 8% stannous fluoride once a week for 4 weeks also prevents caries but is expensive. Special precaution should be taken to avoid swallowing. Topical application is the most effective if done just as the teeth erupt.

Fluoride Toxicity

Chronic toxicity results in mottling of the enamel, brownish-black discolouration of the teeth, joints pain and stiffness, osteosclerosis of the spine and pelvis. Crippling fluorosis is characterised by thickening of the cortex of long bones and bony exostoses specially in the vertebrae.

Acute toxicity could result from accidental or suicidal overdose often due to ingestion of fluoride-containing rat poisons. 2.5-5 gm is the lethal dose in adults. Manifestations include nausea, vomiting, diarrhoea, hypotension, hypocalcaemia, hypomagnesaemia, cardiac arrhythmias and acidosis.

Treatment

- Vomiting should be induced and gastric lavage should be given with fluids containing calcium.
- Cardiac arrhythmias should be treated.
- Correction of acid base imbalance.
- Alkaline diuresis to enhance fluoride excretion.

Prevention of caries Caries can be largely prevented by the following measures:

1. Resistance of the host can be increased by fluoride therapy.
2. Oral flora to be controlled by antiplaque agents.
3. Soluble carbohydrates present in ice-creams, sweets, chocolates, etc.—the substrate for bacterial growth—should be avoided.
4. 'In-between' eating habits should be reduced.
5. Public should be educated regarding the proper use of toothbrush, dentifrices and prevention of caries.

DRUGS USED IN DENTAL PLAQUE

Plaque is the soft, non-mineralised bacterial deposit formed on inadequately cleaned

teeth. Proteins in saliva adhere to the surface of the enamel. Microorganisms from oral cavity colonise on these to form a plaque. As in caries, poor oral hygiene and carbohydrate rich food encourage plaque formation when a plaque gets mineralised, it is called a dental calculus or tartar.

Treatment All plaque should be removed as quickly as possible. The virulent microorganisms of the plaque flora like *Streptococcus mutans* and *Streptococcus sobrinus* are associated with the pathogenesis of caries and many periodontal diseases. These organisms should be controlled either by a suitable antibacterial agent or altering tooth surface to prevent the bacterial attachment to the plaque. Scaling is done to remove the plaque.

Antibacterial Agents

Though penicillins, erythromycin and tetracyclines are effective in controlling plaque, antibiotics which are not absorbed from the oral mucosa should be preferred. Vancomycin, kanamycin, bacitracin and polymyxin-B are used as topical mouthrinses or gels. Controlled delivery systems containing tetracyclines for intra pocket insertion, effectively suppresses periodontal pathogens. However, long-term use of antibiotics should be avoided because of the risk of toxicity.

Other agents that can be used in plaque control are:

1. **Bis-biguanides** Chlorhexidine (page 380) is the most effective anti-plaque and antigingivitis agent. Chlorhexidine gluconate 0.12–0.2% solution is used twice daily for rinsing—15 ml solution is retained for 30 seconds in the mouth and then spat out. For the next 30 minutes, eating, drinking and rinsing the mouth should be avoided. Chlorhexidine binds to oral tissues and is slowly released for about 12 hours.

Mechanism of action—Chlorhexidine is bacteriastatic in low concentrations but bactericidal at higher concentrations. Chlorhexidine binds to the bacterial cell wall and interferes with the uptake of sugars by the bacteria. Higher doses cause precipitation of intracellular proteins leading to cell death. Long-term use of chlorhexidine can cause yellowish brown staining of the teeth, mucosal soreness, desquamation and occasionally altered taste sensation. However, systemic side effects are unlikely since chlorhexidine is used topically. Alexidine can also be used.

Uses

- a. Bisbiguanides are used as mouthrinses, gels and in dentifrices for the control of plaque and gingivitis.
 - b. Chlorhexidine mouth wash is also used to disinfect the oral cavity before dental procedures.
 - c. Ulcerative gingivitis.
 - d. Following oral surgery and denture insertion.
 - e. Prophylactically in immunocompromised patients like those with leukaemia, AIDS and agranulocytosis.
2. **Fluorides** Stannous fluoride mouth rinses or gels are effective in plaque control and make the gums healthier. Fluorides inhibit enzymatic reactions involved in glycolysis.
 3. **Oxygenating agents** like hydrogen peroxide (page 381) and sodium perborate. These compounds act by liberating nascent oxygen.
 4. **Halogens** Halogen releasing compounds like chlorophors and iodophors are used in many antiseptic mouthwashes. Chlorine dioxide and povidone iodine have been widely used—but these are not popular because of their unpleasant taste.

5. *Other compounds*

- Other antiseptics like **phenol** and its derivatives **hexylresorcinol** and **thymol** are used in many anti-plaque mouthrinses. But their properties like disagreeable taste, rapid discolouration and poor solubility make them less preferred.
- A combination of oils including **thymol** (0.06%, **eucalyptus oil** (0.09%), **menthol** (0.04) and **methyl salicyte** (0.06%) in an alcohol based vehicle is found to be useful in inhibiting plaque. These oils act by inhibiting bacterial enzymes and alcohol acts on the bacterial cell wall. The combination is useful in reducing plaque and gingivitis.
- Detergents like **sodium lauryl sulphate** have also been used in several mouthrinses.
- Nonionic bisphenols—**Triclosan** is a germicidal used in toothpaste and in other dental preparations. It has a wide antibacterial spectrum including many gram positive and gram negative bacteria. It causes leakage in the bacterial cell membrane leading to bacterial cell lysis. It is retained in the dental plaque for 8 hours. Triclosan also inhibits gingivitis. When triclosan is incorporated in a polyvinyl copolymer its antibacterial activity improves. Therefore triclosan is used along with the copolymer in toothpaste and is found to be useful in controlling plaque and calculus formation.

DENTAL DESENSITISING AGENTS

Dentin hypersensitivity is a common problem affecting millions of people all over the world. Pain could be evoked by mechanical, chemical or thermal stimuli, i.e. the patient experiences pain while eating hot and cold, sweet or sour food or even while brushing the teeth. The

hypersensitivity is due either to loss of enamel or exposure of the root surface. Loss of enamel may follow mechanical wear or chemical erosion due to acidic food. The root surface gets exposed due to gingival recession as seen in old age, incorrect toothbrushing habits or chronic periodontal diseases.

An ideal desensitising agent should be non-irritant, non-toxic, painless, rapid acting, easy to use and have a long-lasting effect. At present no such single agent is available. Hence multi-modal approach could be employed depending on the severity.

Dental Desensitising Agents are

1. *Agents occluding dentinal tubules:* Potassium nitrate, Potassium oxalate, Calcium hydroxide, Fluorides, Sodium citrate, Formaldehyde
2. *Agents precipitating proteins:*
 - a. *Astringents*
Silver nitrate, Zinc chloride
 - b. *Precipitating tubule proteins causing occlusion*
Strontium chloride, Formaldehyde
3. *Tubule sealants:* 4-Methacryloxyethyl trimellitate
4. *Physical methods:* Restorations—Glass ionomer cements, composites; Laser sealing of the tubule

1. Agents Occluding Dentinal Tubules

Five per cent potassium nitrate used daily is effective in 4 weeks as a desensitising agent. It acts by occluding the dentinal tubules through crystallisation. Used as a toothpaste twice a day, potassium nitrate is a popular desensitising agent.

SENQUEL, SENQUEL AD, THERMO SEAL, Potassium nitrate 5%.

Calcium hydroxide supplies calcium ions which hasten remineralisation of the exposed

dentin. But it has to be applied by a dentist and may require repeated application as the effect is short lived.

Fluorides High doses of fluorides used as dentifrices act by hardening the dentin surface and is claimed to be effective in 3-4 weeks. Fluoride iontophoresis (using 2% NaF) may be employed to occlude the dentinal tubule. The procedure is immediately effective but is expensive and may require repetition.

2. Agents Precipitating Proteins

Astringents—*Silver nitrate* and *zinc chloride* act by precipitating proteins and were used earlier. But they cause permanent staining of the teeth, are toxic to the gingiva and pulp and are therefore not preferred.

Strontium chloride and *formaldehyde* act by precipitating proteins within the tubules occluding them. They have been used in the form of dentifrices in the past.

3. Tubule Sealants

The newer agents including 4-methacryloxyethyl trimellitate have been tried as desensitizers.

4. Physical Methods

Restorations to cover the dentinal tubules using glass ionomer and composites are found to be effective in patients with eroded gingiva. A combination of glass ionomer and composite resins is more beneficial when compared to either agents used alone. In patients with gingival loss, soft tissue grafts cover the exposed dentin to relieve the sensitivity.

EMERGENCIES IN DENTAL PRACTICE

A dentist can come across several life threatening emergencies in dental practice although not frequently. Several factors have contributed to an increase in the rate of these emergencies like –

1. A rise in geriatric population and a consequent increase in the number of elderly patients seeking dental therapy.
2. the tendency for longer dental appointments.
3. an increase in the use of drugs in dentistry.

Dentists therefore, must be equipped with adequate knowledge for appropriate management of such situations, because they can be life threatening. Treatment and prevention of some of the common emergencies that may be encountered in dental practice are discussed below.

1. Anaphylaxis

Anaphylaxis: is an immediate type of hypersensitivity reaction and can occur following the use of drugs, and allergens. Anaphylaxis is more common following parenteral administration of drugs. Though it can be induced by any or all drugs, some drugs like lignocaine, penicillins, cephalosporin and sulfonamides are more likely to induce anaphylaxis. Antigen – antibody complexes bind to the mast cells leading to the degranulation of these mast cells. This results in the release of massive amounts of histamine and other inflammatory mediators which are responsible for the symptoms of anaphylaxis. Symptoms usually occur within minutes of exposure to the offending agent. Signs and symptoms include—

- Cutaneous – itching at the site of injection and/or generalized itching, swelling of subcutaneous tissues, eyelids, lips and tongue.
- Respiratory—wheezing due to bronchospasm, cough and laryngeal oedema.
- Cardiovascular – hypotension resulting in dizziness and in more severe cases loss of consciousness.

When severe, it can be rapidly fatal. Hence, every medical and dental practitioner must know to manage anaphylaxis.

Treatment – should be immediate.

- Intramuscular injection of adrenaline 0.5ml of 1:1000 solution is life saving. The dose may be repeated every 10 minutes if required. If hypotension is not significant, adrenaline may be injected subcutaneously. If anaphylaxis is very severe, 0.5 ml adrenaline may even be given intravenously slowly. Dose may be repeated if needed after 5 to 10 minutes.
- The patient should be put in reclining position.
- Arrangement should be made to transfer the patient to the nearest emergency ward.
- High flow oxygen should be given.
- Vital signs should be carefully monitored.
- Cardiopulmonary resuscitation may be done if required.
- Intravenous hydrocortisone hemisuccinate 100-200 mg will be needed in severe cases particularly in asthmatics.
- An antihistamine like chlorpheniramine 20 mg IM or diphenhydramine 50 mg IM may be given as an adjuvant. Antihistamines should be continued orally for 2 to 3 days.
- Intravenous fluids should be started. Vasopressors like dopamine may be given if needed.

2. Uncontrolled Bleeding

Most dental procedures cause some bleeding. It is mostly minor and local application of mild pressure for 10-20 seconds would generally arrest bleeding. If bleeding continues, a cotton swab dipped in 1% adrenaline solution may be used as a pack. Ice pack for a few minutes may also be tried. Gel foam may be used in more severe bleeding.

Uncontrolled bleeding following dental procedures may be seen in one of the following-

1. Patients on antiplatelet drugs or those with thrombocytopenia due to any cause.
2. Patients on anticoagulant therapy
3. Haemophiliacs
4. Vitamin C deficiency
5. Long-term glucocorticoid therapy

They should be controlled as follows:

- Reduction in the platelet count or impaired platelet function due to antiplatelet drugs can result in severe bleeding. Appropriate measures should be taken to correct the above before taking the patient for surgery or other dental procedures associated with bleeding. If the patient is on drugs that inhibit platelet aggregation, consult the physician 1-2 weeks before an elective surgery and under his guidance such drugs may be withdrawn temporarily. Duration of antiplatelet effects of clinically used drugs like ticlopidine and clopidogrel is around 7 to 10 days. Therefore these drugs should be withdrawn about 7-8 days before the procedure and prothrombin time should be brought down to 1½ to 2 times the control value. The antiplatelet drugs should be restarted after adequate healing has occurred. Even minor bleeding including petichiae and ecchymoses should be watched for.

- If thrombocytopenia is due to any other cause, platelet transfusion may be required before any surgical procedure is undertaken in consultation with a physician.

- If the patient is on anticoagulants, they may be temporarily withdrawn or the dose reduced in consultation with a physician.

- Drugs with antiplatelet effects like NSAIDs should be used carefully.

- Vitamin C deficiency as such may result in bleeding from the gums and may enhance bleeding from dental procedures and also impair wound healing. Local application of adrenaline pack or pressure may be needed following minor dental procedures. Major dental procedures should be done after the correction of vitamin C deficiency.

- Glucocorticoid therapy—Patients on long-term glucocorticoid therapy may bleed more and wound healing may be impaired. Wounds are also more susceptible to infections. Adequate local haemostatic measures should be taken.

- Haemophiliacs—are deficient in coagulation factor VIII and are therefore likely to bleed more even from minor dental procedures. Factor VIII should be supplemented before the dental procedure and adequate local haemostatic measures should be taken.

3. Unconsciousness:

Patients with no response to stimuli need immediate attention.

Unconsciousness in dental practice may be due to one of the following causes-

a. Vasovagal attack/syncope/fainting

Vasovagal attack is the transient loss of consciousness due to a painful or an emotional stimulus. Pathophysiology involves an autonomic imbalance. In response to the stimulus, the vagus is stimulated which in turn results in bradycardia, reduced cardiac output and hypotension accompanied by peripheral vasodilation. Hypotension reduces the blood supply to the brain leading to cerebral hypoxia which in turn results in unconsciousness. However, the patient recovers in 1-2 minutes because the sympathetic system gets activated and reverses the symptoms.

Treatment:

- Loosen tight clothing to facilitate breathing.
- Elevate feet to increase venous return.
- Give cold compress to promote peripheral vasoconstriction and increase venous return.
- Oxygen inhalation may be given.

b. *Hypoglycaemia* – is to be expected in patients with diabetes mellitus. Signs and symptoms include sweating, tachycardia, tremors, blurred vision, weakness, hunger, confusion and drowsiness leading on to unconsciousness. In mild hypoglycaemia, oral administration of sugar or sugar containing fruit juices are sufficient to overcome the symptoms. In unconscious patients, 50 ml of 50% dextrose is given intravenously – usually patient recovers within a few minutes.

c. *Seizures* – see below.

d. *Arrhythmias* – may be

- Bradycardias-transient loss of consciousness with slow irregular heart rate of <40 beats/minute.
- Tachycardias-Heart rate >150/minute may be associated with fatigue, breathlessness and syncope

e. Cardiac arrest is stoppage of the heart, also called cardiac standstill. If revived on time the heart may recover.

Clinical features – Loss of consciousness
– Absence of pulses
– Gasping or absence of breathing.

Management

- Maintain airway – turn the patient's head to a side, use mouth gag.
- Raise the foot end.
- Mouth to mouth respiration to be given-take 4 quick, deep breaths and then exhale into the patient's mouth. This has to be repeated 12 times per minute.
- As an alternative, bag mask may be used with 100% oxygen.
- External cardiac massage to be given at 60 chest compressions per minute.
- 0.5ml of 1:1000 solution of adrenaline should be injected intravenously or in more severe cases intracardiac adrenaline injection may be needed.

- Medical assistance should be taken at the earliest possible.

4. Seizures

Patients can develop symptoms ranging from brief lapses of awareness to generalized convulsions usually lasting for less than 5 minutes.

(i) If tonic clonic seizures start during a dental procedure:

- Remove instruments or dentures if any from the oral cavity.
- Place a gag or a padded tongue depressor in the mouth between the teeth.
- Turn the head to a side this keeps the airway clear and prevents the tongue from falling back.
- If seizures continue, 10 mg diazepam should be given intravenously.
- Whenever possible dental procedure may be postponed.
- If the patient continues to have seizures despite treatment, physician should be called and managed as status epilepticus. (see page 153)

(ii) Absence seizures—There is sudden impairment of consciousness associated with staring. The patient stops all on-going activities but recovers within a few seconds. The episode lasts for a brief period, generally less than 30 seconds. It only requires reassurance. Patient should be advised to see a physician later.

(iii) Atonic seizures—also called drop attacks are characterised by sudden loss of postural tone and the head may drop for a few seconds or the person may drop to the ground for no obvious reasons. The patient recovers usually within a few seconds and only requires reassurance particularly if the patient is already on treatment by a physician.

5. Ischemic Heart Disease

Ischemic heart diseases include angina and myocardial infarction.

Angina pectoris is the principle symptom of ischemic heart disease and is characterised by sudden severe substernal pain or discomfort which may radiate to the left shoulder or medial aspect of the left arm. It is precipitated by stress and anxiety. Most dental procedures are painful and may evoke some anxiety. Therefore during a dental procedure, IHD patients may experience an episode of exertional angina or very rarely develop myocardial infarction.

1. IHD patients should be taken up for early appointments in the morning and not made to wait.
2. Patients with known IHD should be asked to carry their rescue medication i.e nitroglycerine tablets for sublingual use to the dental clinic. In patients with moderate to severe angina, prophylactic nitroglycerine (0.5mg tab sublingually) may be used 5 minutes before starting the dental procedure.
3. If a patient gets an acute episode of angina during a dental procedure.
 - Stop the dental procedure for a few minutes
 - Administer tab nitroglycerine 0.5mg sublingually. It relieves pain in 2-5 minutes.
 - Monitor pulse and BP.
 - If pain is not relieved in 8-10 minutes, nitroglycerine dose may be repeated. (maximum of 3 tablets in 15-20 minutes). Even then, if the pain does not subside, there are chances that the patient may be going into myocardial infarction. Immediate medical attention should be sought.

Myocardial Infarction

Signs and symptoms – Severe substernal pain, radiating to the left shoulder, with nausea,

vomiting, palpitation, and sweating, patient appears pale and apprehensive. Patient should be shifted to emergency care at the earliest possible. While such arrangements are being done, injection pethidine 50 mg or morphine 10 mg should be given intramuscularly. Patient should be made to swallow a tablet of aspirin 300 mg. Oxygen inhalation should be given if possible. For treatment see page 108.

6. Shock

Treatment of shock is discussed in page 121. Intravenous fluids are given in almost all the different types of shock. Therefore a knowledge of the different IV fluids available is important.

Intravenous Fluids

Intravenous fluids are sterile solutions meant for intravenous administration. The content and quantity of solute varies. Intravenous fluids are used for replacement of fluid, electrolytes and nutrition. There are different types of IV fluids to be given depending on the patient's requirements.

Types of IV Solutions

Intravenous solutions are of 3 types depending on osmolality - *isotonic*, *hypotonic* or *hypertonic*. Fluids having an osmolality nearly equal to that of extracellular fluid (ECF) or if the electrolyte content (cations + anions) is nearly equal to 310 mEq/L – they are considered isotonic.

Isotonic-electrolyte content = 310 mEq/L

Hypotonic-electrolyte content < 250 mEq/L

Hypertonic-electrolyte content > 375 mEq/L

(Plasma osmolality is nearly equal to 300 m mol / L. Osmolality of 10% dextrose is 505 m mol / L.)

Isotonic Fluids As isotonic fluids have an osmolality nearly equal to that of ECF, they

do not alter the size of RBCs (neither shrink nor swell). One litre of isotonic solution expands ECF by 1 litre. But it quickly diffuses into the ECF compartment and therefore around 3 litres of isotonic fluid is needed to replenish volume of one litre of lost blood. However patients with hypertension and cardiac failure need careful monitoring to avoid fluid overload. Isotonic solutions include normal saline and lactated ringer solution.

Normal saline solution – 0.9 % sodium chloride. It is used in hyponatraemia. It should be avoided in heart failure, pulmonary oedema and renal impairment.

Lactated ringer solution contains potassium, calcium and sodium chloride. It is used to correct dehydration, hyponatraemia and to replace gastrointestinal fluids. Many other similar solutions are available with minor changes in the electrolyte content.

Hypotonic fluids Hypotonic fluids replace cellular fluid because they are hypotonic as compared to plasma. Half normal saline (0.45% sodium chloride solution) is the commonly used hypotonic solution but other electrolyte solutions are also available. Hypotonic sodium solution is used in hypernatraemia and other hyperosmolar conditions. Overdosage can result in intravascular fluid depletion, hypotension, cellular edema and later cell damage.

Hypertonic fluids Five percent dextrose in normal saline or lactated ringer's solution or in hypotonic solution has osmolality more than ECF 45 to 50%. Dextrose solution may be administered in hypoglycaemia or to supplement calories. Since these solutions are strongly hypertonic, they should be injected into central veins for rapid dilution. Hypertonic saline solutions draw water from the cells and the cells shrink. They should be injected slowly and carefully to avoid ECF volume overload.

7. Diabetic Ketoacidosis

May be precipitated by infection, stress or trauma. It is more common in patients with insulin – dependent diabetes mellitus. Diabetic ketoacidosis is a medical emergency and can be life threatening. Insulin deficiency results in severe hyperglycaemia (600 - 800mg/dl) and excessive production of ketone bodies.

Clinical features include metabolic acidosis, dehydration with loss of sodium and potassium in the urine causing electrolyte imbalance, impaired consciousness and hyperventilation – may proceed to coma. Diabetic ketoacidosis should be suspected when the patient has IDDM, diabetes is uncontrolled, patient is under stress, or has infection and develops the above signs and symptoms.

Treatment

- Correction of hyperglycaemia – intravenous regular (plane) insulin 0.1U/kg bolus followed by 0.1 U/kg/hour by continuous IV infusion till the patient recovers. Once the patient has fully recovered, insulin should be administered subcutaneously 30 minutes before stopping the infusion.
- Correction of dehydration – Fluid and electrolyte replacement are important. Normal saline infusion 1 litre in the first hour and then 1 litre over the next 4 hours and then the quantity can be titrated based on the severity of dehydration.
- Correction of acidosis – Sodium bicarbonate may be needed in some patients with severe acidosis.
- Potassium – Rapid correction of hyperglycaemia may result in the movement of potassium into the cells resulting in hypokalemia. 10-20 mEq/hour potassium chloride is added to the drip. When serum

phosphate is also low, potassium biphosphate may be given to supplement both potassium and phosphorus.

Hyperglycemic, hyperosmolar, nonketotic, coma – Severe hyperglycaemia and glycosuria result in severe dehydration and increased plasma osmolality leading to coma and has a high mortality rate. The treatment is similar to ketoacidosis with correction of fluid and electrolyte balance and plane insulin.

8. Acute Addisonian Crisis

Acute Addisonian crisis is an emergency condition that could be precipitated by an infection or sudden withdrawal of steroids after long-term administration. Proper drug history is therefore very important. If the patient has been on glucocorticoids like (prednisolone) for more than 2 weeks, it should be continued. The dentist should make sure that the patient receives his dose of glucocorticoid on the day of dental procedure particularly if it is a major procedure. Symptoms include nausea, vomiting, weakness, hypotension, dehydration, hyponatraemia and hyperkalaemia. Intravenous hydrocortisone hemisuccinate 100 mg bolus followed by infusion 100 mg every 4-6 hours is given immediately. The dose may be repeated depending on the patient's condition. Once the patient recovers, switch over to oral preparations. Immediate correction of fluid and electrolyte balance is important. When acute adrenal insufficiency is not confirmed, dexamethasone (4mg IV) should be used in place of hydrocortisone because dexamethasone does not interfere in the estimation of hydrocortisone levels for diagnosis.

9. Tetany

Tetany is due to hypocalcaemia (Page 373): Other features of hypocalcaemia include muscle cramps, paraesthesias, laryngospasm

and in more severe cases – convulsions. Slow intravenous injection of 5-20ml of 10% calcium gluconate relieves tetany. Care should be taken to inject calcium slowly because rapid intravenous injection of calcium can cause cardiac arrhythmias which can be fatal.

10. Status Asthmatics

An acute attack of bronchial asthma may be precipitated by dental procedures them-

selves, the stress or anxiety due to them or the drugs and materials used in such procedures. A known asthmatic patient should be told to attend the clinic with bronchodilator inhaler which the patient has been taking - preferably salbutamol. An acute attack should be treated with 1-2 puffs of 100-200 µg salbutamol (Page 215).

Acute severe asthma or status asthmatics needs immediate treatment (See Page 219).

Appendices

□ **APPENDIX-1—IMPORTANT DRUG INTERACTIONS**

□ **APPENDIX-2—PRESCRIPTION WRITING**

APPENDIX-1

IMPORTANT DRUG INTERACTIONS

<i>Interacting drugs</i>	<i>Consequence</i>	<i>Pharmacological basis</i>
1. β -blockers + hydralazine/frusemide	$\uparrow$ β blocking effect	$\downarrow$ metabolism of propranolol
2. β -blockers + insulin	i. β -blockers mask palpitation, the most important warning symptom of hypoglycaemia ii. They prolong recovery from hypoglycaemia	- Blockade of cardiac β receptors - Block hepatic glycogenolysis mediated by β_2 receptors; homeostatic mechanisms are blocked
3. Propranolol + ephedrine	$\uparrow$ BP	As β receptors are blocked, unopposed stimulation of α receptors by ephedrine elevates BP
4. Propranolol + verapamil	May cause heart block resulting in cardiac arrest	Both drugs depress conducting tissues of the heart and have negative inotropic effects
5. Calcium channel blockers + phenytoin/rifampicin	$\downarrow$ effects of calcium channel blockers	Both increase metabolism of calcium channel blockers by enzyme induction
6. Digoxin + hydrochlorothiazide	Digoxin toxicity	Thiazides cause hypokalaemia which in turn aggravates digoxin toxicity
7. Digoxin + quinidine	Digoxin toxicity	Quinidine displaces digoxin from tissue binding sites and inhibits digoxin excretion
8. Digoxin + antacids/sucralfate/metoclopramide	$\downarrow$ bioavailability of digoxin	Reduce absorption of digoxin

Contd...

Contd...

<i>Interacting drugs</i>	<i>Consequence</i>	<i>Pharmacological basis</i>
9. Bile acid-binding resins + Frusemide/ thiazides/thyroid hormones	↓ bioavailability	Bind and prevent absorption of orally administered drugs
10. Anticoagulants + phenylbutazone	Anticoagulant toxicity	Inhibit anticoagulant metabolism
11. Warfarin + aspirin	i. Anticoagulant toxicity ii. Bleeding from aspirin induced peptic ulcer	• Aspirin displaces warfarin from binding sites • Inhibition of platelet aggregation by aspirin potentiates anticoagulant effect • Aspirin induced gastric erosion and ulcers may bleed more due to anticoagulant effects
12. Alcohol + disulfiram <i>Other drugs that produce disulfiram like effects</i> cephalosporins, metronidazole, sulfonyleureas	Antabuse reaction	Disulfiram inhibits aldehyde dehydrogenase resulting in accumulation of acetaldehyde
13. Alcohol + CNS depressants like opioids/antidepressants/antihistamines/hypnotics	Profound CNS depression	CNS depressant effect gets added up
14. Carbamazepine + haloperidol/oral contraceptives/corticosteroids	Decreased efficacy of interacting drugs	Carbamazepine is an enzyme inducer—enhances metabolism of interacting drugs
15. Carbamazepine + cimetidine/erythromycin/INH/ketoconazole	Decreased carbamazepine metabolism	Inhibition of drug metabolising enzymes by interacting drugs
16. Phenytoin + carbamazepine	Decreased effects of both	Phenytoin and carbamazepine increase each other's metabolism
17. Phenytoin + chloramphenicol/cimetidine/warfarin	Phenytoin toxicity	The interacting drugs inhibit phenytoin metabolism
18. Phenytoin + steroids/doxycycline/theophylline	Phenytoin increases metabolism of interacting drugs	Phenytoin is an enzyme inducer
19. Barbiturates + other CNS depressants	Profound CNS depression	CNS depression gets added up
20. Barbiturates + calcium channel blockers/corticosteroids/ketoconazole/oestrogen/chloramphenicol/tricyclic antidepressants	Decreased efficacy of interacting drugs	Barbiturates are enzyme inducers. They enhance the metabolism of interacting drugs

Contd...

Contd...

<i>Interacting drugs</i>	<i>Consequence</i>	<i>Pharmacological basis</i>
21. Tricyclic and related antidepressants + carbamazepine/rifampicin	Increased metabolism of antidepressants	Carbamazepine and rifampicin are enzyme inducers
22. Tricyclic antidepressants + SSRIs like fluoxetine and paroxetine	Decreased metabolism of antidepressants	SSRIs inhibit metabolising enzymes
23. Tricyclic antidepressants + MAO inhibitors	Hypertensive crisis	Uninhibited action of catecholamines due to inhibition of MAO
24. Levodopa + phenothiazines	Decreased anti-parkinsonian effect	Phenothiazines block dopamine receptors
25. Levodopa + pyridoxine	Inhibits antiparkinsonian effect	Pyridoxine enhances peripheral decarboxylation of levodopa
26. Lithium + diuretics	Lithium toxicity	Decreased excretion of lithium
27. NSAIDs + frusemide	Blunting of diuretic effect	PG inhibition may result in salt and water retention
28. Aspirin + warfarin/phenytoin/ sulfonylureas	Toxicity of co-administered drugs	Aspirin displaces these drugs from protein binding sites
29. Quinolone antibiotics + sucralfate/antacids	↓ bioavailability	Reduced gastrointestinal absorption of quinolones
30. Quinolones + theophylline/caffeine	Toxicity due to theophylline/caffeine	Quinolones inhibit the metabolism of theophylline/caffeine
31. Chloramphenicol + phenytoin/sulfonylureas	Toxicity due to phenytoin/sulfonylureas	Chloramphenicol decreases metabolism of these drugs
32. Rifampicin + oestrogens/corticosteroids/sulfonylureas/theophylline	Therapeutic failure	Rifampicin is an enzyme inducer and increases the metabolism of other drugs
33. Antacids + quinolones/salicylates/tetracycline	↓ bioavailability	Antacids may adsorb drugs and reduce their absorption
34. Antacids + sucralfate	Therapeutic failure of sucralfate	Sucralfate acts in acidic pH while antacids make the gastric pH alkaline
35. Allopurinol + 6-mercaptopurine	6-mercaptopurine toxicity	Allopurinol inhibits xanthine oxidase which metabolises 6-mercaptopurine
36. Piperazine citrate + pyrantel pamoate	Therapeutic failure	Piperazine causes hyperpolarization while pyrantel causes depolarization. They antagonise each others effects

APPENDIX-2

PRESCRIPTION WRITING

The Prescription is a written order by a physician to the pharmacist to prepare and/or dispense specific medication for a specific patient. A specific pattern should be followed in writing prescriptions, in order to avoid errors and to safeguard the interests of the patient. Moreover the fact that it is a medicolegal document makes it all the more important to be accurate and precise.

The following points should be remembered in writing a prescription:

1. The writing should be legible.
2. Indelible ink should be used in writing.
3. Abbreviations should be avoided.
4. In writing quantities—decimals should be avoided; when inevitable, zero should be used—0.1 for .1.
5. Less than 1 gm—should be written as milligrams, e.g. 200 mg and not 0.2 g. No abbreviation should be used for micrograms and units.
6. Blank space should be avoided between direction and the signature of the doctor. If blank space is present, it should be striked off to avoid misuse of the space to obtain drugs illegally.

PARTS OF THE PRESCRIPTION

1. Date of writing the prescription.
2. Address of the prescriber—preferably prescriptions are written on the letter pad with doctor's name and address printed at the top.
3. Name, age, sex and address of the patient.
4. Superscription—the symbol $\mathcal{R}$ meaning 'take thou' is also considered as an invocation to the Greek gods of healing—Jupiter and Horus.
5. Drug name and strength. This is the body of the prescription—also called inscription. Abbreviations should never be used.
6. Directions to the pharmacist (subscription)—consists of instructions for compounding if any and the quantity to be supplied.
7. Directions to the patient—should be clear and should indicate the quantity, frequency, time, route of administration and other information relevant to the preparation. If a drug is meant only for external application or needs to be shaken well or mixed before using—such instructions should be mentioned.
8. Signature of the prescriber—the prescriber should sign along with registration number.

TYPES OF PRESCRIPTIONS

1. *Precompounded prescription* orders for a drug manufactured by a pharmaceutical company, has a trade name and is available for use.
2. *Compounded or extemporaneous prescription* the physician directs the pharmacist to compound a preparation. The ingredients, their quantity and the form of preparation (like mixture, powder or ointment) is chosen by the physician and instructed accordingly.

MODEL PRESCRIPTION

Dr Vaidya
Highland
Mangalore

July 10, 2007

Tel No. _____

Ramu
No. 7, Kankanady
Mangalore

Male

Age: 35 years

R̄

Tab Roxithromycin 150 mg

Dispense 10 tablets

Label—Take 1 tab orally twice a day, 30 minutes before food.

Signature

Regn. No.

SOME COMMONLY USED LATIN ABBREVIATIONS IN PRESCRIPTIONS

Abbreviation	Latin derivation	Meaning in English
o.d.	onus in die	once a day
b.d.	bis in die	twice a day
b.i.d.	bis in die	twice a day
t.i.d.	ter in die	three times a day
t.d.s.	ter die sumendum	three times a day
q.i.d.	quarter in die	four times a day
h.s.	hora somni	at bed time
stat	statim	at once
s.o.s.	si opus sit	if necessary
q.s.	quantum sufficit	A sufficient amount
p.o./po	per os	by mouth
ung	unguentum	ointment
caps	capsula	capsules
Tab	Tabella	Tablet
a.c.	ante cibum	before food

Further Reading

1. Katzung BG: *Basic and Clinical Pharmacology* (9th edn.) Mc Graw Hill International Edition 2004.
2. Satoskar RS, Bhandarkar SD, Ainapure SS: *Pharmacology and Pharmacotherapeutics*. Revised eighteenth edition 2005.
3. Tripathi KD: *Essentials of Medical Pharmacology* (5th edn.) Jaypee Brothers: New Delhi, 2003.
4. Barar FSK: *Essentials of Pharmacotherapeutics* (3rd edn.) S. Chand & Company Ltd. New Delhi, 2000.
5. Lawrence DR, Bennet PN, Brown MJ: *Clinical Pharmacology* (9th edn). Churchill Livingstone: London, 2002.
6. Rang HP, Dale MM, Ritter JM: *Pharmacology* (5th edn.) Churchill Livingstone: New York, 2003.
7. Hardman JG, Limbird LE *et al*: Goodman and Gilman's: *The Pharmacological Basis of Therapeutics* (10th edn.) MC Graw Hill: New York, 2001.
8. Craig CR; Robert E. Stitzel *Modern Pharmacology with Clinical Applications* (6th edn). Little Brown: Boston, 2003.
9. Park K. Park's: *Text book of Preventive and Social Medicine* (17th edn.) M/s Bharanidas Bhanot, Jabalpur, 2002.
10. Page CP, Curtis MJ *et al*: *Integrated Pharmacology* (2nd edn) Mosby, London 2002.
11. Martindale: *The complete Drug Reference* 33rd edn.) Pharmaceutical Press, 2002.
12. Mary J. Mycek, Richard A. Harvey, Pamela C. Champe, Bruce D. Fisher, *Lippincott's illustrated Reviews* (2nd edn.) Lippincot-Raven Publishers, 1992.
13. Harrison's *Principles of Internal Medicine* 14th edition, Mc Graw Hill: 1998, International edition.
14. Robert E. Rakel, *Conn's Current therapy* 2000 W.B. Saunders Company, Pennsylvania.

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